

A STUDY OF THE ANATOMY,

PHYSIOLOGY AND SURGERY OF THE

VAGUS NERVES IN

THE ABDOMEN

by

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Thesis submitted for the degree of Ch.M.

University of Edinburgh

October 1969.



1/10/69.

It is hereby declared that all animal experimental work, the assembly and analysis of all laboratory and clinical data (with the exception of Table II, 2 and Figures A, 5 and 6) and the composition of the thesis itself has been entirely the work of the author.

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ACKNOWLEDGMENTS

Professor Sir John Bruce, Mr. C. W. A. Falconer, Mr. A. N. Smith and Dr. W. Sircus have provided support and the opportunities to perform these studies.

The co-operation and facilities of the Gastric Surgery Follow-up Clinic of the Western General Hospital have been freely provided by Mr. W. P. Small.

Dr. W. R. Waddell, Dr. B. C. Paton and Dr. F. Kern of the University of Colorado Medical Center provided facilities for laboratory and animal experiments and gave active encouragement throughout.

Permission to include illustrations from ancient and valuable anatomy texts was granted by Mr. J. R. Cameron, President of the Royal College of Surgeons of Edinburgh. Miss D. U. Wardle, Chief Librarian of the College traced these books, and the material was photographed by Mr. J. Bathgate.

Histograms in Part III were provided by Mr. C. Shepley and black and white photography by Mr. J. Patterson and Mr. S. Baker. Illustrations other than the above were drawn by the author.

Professor K. W. Donald and the staff of the Department of Medicine kindly provided access to the Olivette Programma 101 with which the statistics were calculated.

The secretarial assistance of Miss I. Scott, Mrs. R. Zeitlin, Miss J. Cochrane and Mrs. E. Hunter is gratefully acknowledged.

PUBLICATIONS

Material in this thesis has been incorporated into the following publications:-

1. A Study of the Variations of the Abdominal Vagi.
C. V. Ruckley. British Journal of Surgery, 51: 569, 1964.
2. Selective Vagotomy: A Review of the Anatomy and Technique in 100 Patients. C. V. Ruckley, C. W. A. Falconer, W. P. Small and A. N. Smith. British Journal of Surgery, 1969 - In Press.
3. The Effect of Complete and Incomplete Antrectomy upon Vagally-stimulated Secretion in dogs. C. V. Ruckley and W. R. Waddell. Surgery, 1969 - In Press.
4. Carbon-14-labelled Polyethylene Glycol as a Gastric Secretory Marker. C. V. Ruckley and F. Kern, 1969 - In Preparation.
5. The Clinical Application of the Examination of Gastric Secretory Function. C. V. Ruckley and W. Sircus. Progress in Gastroenterology. Editor: G. B. Jerzy-Glass - In Press, 1969.
6. Figures I, 13 and I, 19. Bailey and Love's Short Practice of Surgery. Editors: A. J. H. Rains and W. M. Capper, 14th Edition, 1968.

S U M M A R Y

The history of our knowledge of the anatomy of the abdominal vagus nerves is traced from the time of Galen. Variations in the macroscopic distribution of the vagi are described in studies in 12 cadavers and 123 vagotomy operations. A simplified technique for selective vagotomy is presented.

Ways in which the neuro-hormonal mechanisms of gastric secretion affect peptic ulcer surgery; principally the effects of antrectomy upon gastric secretion and upon the interpretation of tests of vagal function are discussed in the light of reviewed material from the literature, secretion tests in post-vagotomy patients and experiments upon the effects of complete and incomplete antrectomy in dogs. Complete antrectomy depresses vagus-mediated gastric acid secretion by 60%. Pepsin output is not affected. An antrectomy of approximately 80 - 90% in dogs results in very variable alteration of the vagus-mediated acid response. The implications for interpretation of the insulin test for completeness of vagotomy are discussed.

The problems of performance and interpretation of the insulin secretion test are discussed. The dose of insulin is critical owing to its conflicting actions of stimulation and inhibition. The results of secretion tests using different doses of insulin in both dogs and humans are presented. Pre-operative insulin tests in 171 patients and post-vagotomy tests in 170 have been studied, together with data upon basal and maximal (M.A.O.) acid outputs. It is concluded that the optimal dose of insulin, both in dog and man is approximately 0.15 units/kg. body weight. Analysis of the insulin test by multiple criteria shows a correlation between both M.A.O. and basal acid and the strength of the insulin response. The insulin test is still preferred as the test for completeness of vagotomy. For interpretation of the/

the insulin test a scoring system is advocated based upon multiple criteria and the timing of the secretory response.

With certain specific exceptions recurrent peptic ulcer does not develop in the presence of complete gastric vagotomy. It is suggested that the per cent risk of a patient developing recurrent ulcer can be graded according to the post-operative secretory data. It may therefore be possible to eliminate the recurrent ulcer risk by elective re-operation in a carefully selected small minority of post-vagotomy patients.

In the clinical studies the early and late complications of vagotomy are studied. A 94% follow-up of a duration of $1\frac{1}{2}$ - 15 years of 260 post-vagotomy patients is presented. Truncal vagotomy (170 cases) and selective vagotomy (86 cases) provide results which are essentially similar in respect of operative morbidity. The incidence of late post-operative diarrhoea in the two groups was 32% (6% severe) and 24% (0% severe) respectively. The incidence of incomplete vagotomy (after vagotomy with drainage) was 44% and 30% respectively. The factors influencing these results and the steps necessary to improve the incidence of failed vagotomy are discussed.

Finally the necessary evaluation of these operations by a randomised controlled trial is discussed in its technical aspects on the basis of our experience over an eighteen month period.

INTRODUCTION

Vagotomy has become the most important operation in the treatment of duodenal ulcer. The scientific foundations of modern peptic ulcer surgery were laid in St. Petersburg where Pavlov became Professor in 1889 and brought to fruition his studies on canine gastro-intestinal physiology which won him the Nobel Prize in 1904. The literature which has accumulated since then is vast, exhausting it would seem, every aspect of the anatomy and physiology of the foregut.

In the face of such academic wealth it may be disconcerting for the clinician to find, when he moves from laboratory to ward that many questions remain unanswered, and that medical and surgical opinion is still deeply divided over the management of peptic ulcer.

The studies described in this thesis were orientated especially towards aspects of anatomy and physiology pertaining to practical problems encountered in the surgical management of patients with ulcer disease: problems whose origins may best be revealed by a glance at the evolution of vagotomy as an operation for peptic ulcer.

The History of Vagotomy

The functional relationship between the par vagum and the stomach was recognised by anatomists of the sixteenth and seventeenth centuries. The subsequent development of our anatomical knowledge is discussed in Chapter 1. Elucidation of the nature of the physiological relationship between stomach and central

/nervous

nervous system awaited the work of Pavlov who showed that vagal section in the dog abolished what he named the 'cephalic phase' of gastric secretion. The earliest surgical attacks upon the vagi were not for duodenal ulcer. According to McCrea (1929) -

" Exner (1911) performed subdiaphragmatic resection of the vagus, and his cases were all tabetics with gastric crises. He considered that the vagus controlled vomiting, and that Foerster's operation (splanchnicectomy) was only of use in cutting off sensation via the splanchnics. He observed on section of the nerves an immediate dilatation, atony, and pylorospasm, and because of the last added to his procedure a gastrojejunostomy or a gastrostomy."

It is only in the past decade that translation of Pavlov's work to human surgery in the shape of vagotomy has achieved almost universal acceptance. Apart from the usual refractory period which separates scientific discovery from its practical application there are two main reasons for this delay.=-

Firstly came the failure to recognise, when Dragstedt first introduced vagotomy upon a reasoned physiological basis for the treatment of duodenal ulcer in 1943, that drainage or resection to relieve stasis was also necessary. Gastroenterostomy, first performed by Wöfler in 1881 for gastric carcinoma, was the

/preferred

preferred operation for duodenal ulcer in the first quarter of this century. It was superceded by partial gastrectomy. Neither of these procedures was regularly combined with vagotomy until the 1940's. Insufficient credit, as Burge (1964) has emphasised, has been accorded to Latarjet who in 1922 had said:-

" En effet, dans tous les cas que nous rapportens, la gastroentero anastamose a été pratiquée en meme temps que l'énervation, soit pour une raison d'ordre mécanique, soit par crainte de voir aggravée l'évolution de l'ulcere à la suite d'un séjour plus prolongé des aliments dans un estomac rendu hypotonique par l'énervation."

Gastric stasis in the undrained vagotomised stomach gave rise to a number of unpleasant symptoms (Dragstedt 1947; Moore, 1948). Epigastric discomfort, distension, the belching of foul wind, vomiting, diarrhoea and recurrent ulcer brought many patients to secondary resection or gastro-jejunostomy. In a series of 736 patients 44% were graded as unsatisfactory (Pollock, 1952). Not surprisingly vagotomy fell into disrepute.

A second reason for this fall from grace was the new vigour which entered civilian surgery in the period following World War II, bringing with it revived popularity for the more radical approach of subtotal gastrectomy for duodenal ulcer. This operation gained ascendancy until its greater operative mortality, its failure to abolish recurrent ulceration and its harvest of undesirable nutritional sequelae could not be ignored.

/Steadily

Steadily gaining ground since its resurrection in the 1950's vagotomy is now being applied with one of two main types of accompanying procedure; gastric drainage and gastric resection. The relative merits of these operations, and their effects on gastric function will be discussed in the physiological and clinical sections of this thesis.

Vagus/Antrum:

A major aspect of gastric physiology with which this thesis deals is that of the relationship between the vagus nerves and the gastric antrum.

Pavlov's teaching of separate and distinct cephalic and gastric phases of secretion has only recently given way to the more complex neuro-hormonal concept in which the direct vagal and indirect gastrin-mediated modes of stimulation are recognised to be synergistic.

Laboratory and clinical studies described in Parts II, III and IV include an analysis of the relevance of this neuro-hormonal interdependence to the design and results of operations for peptic ulcer disease and a review of gastric secretion tests in cases of truncal and selective vagotomy.

Complications of Vagotomy

The great advantage of vagotomy lies in its safety in terms of operative morbidity and mortality. Our own experience is described in Part IV, Chapter 19. It was soon realised that

/vagal

vagal division, even with accompanying drainage, carried its own liabilities. Diarrhoea, of which the incidence and severity has been vigorously debated, is a problem now acknowledged by most reviewers (Collins, Crile and Davis 1948; Palumbo, Pane and Westly 1952; Walters and Mobley 1957; Burge and Pick 1958; Marshall 1964; Schuberth and Westerholm 1965; Nobles 1966; Lynwood-Herrington 1967; Schofield, Watson-Williams and Sourell 1967; Barnes and Williams 1967 and others). Post-vagotomy diarrhoea in its severe form, although uncommon, may be physically and socially incapacitating and, it must be emphasised, is refractory to treatment. This complication is discussed fully in Part IV, Chapter 21.

Cholelithiasis is increasingly being reported as a complication of truncal vagotomy (Griffiths and Holmes 1964, Neilson 1964, Nobles 1966, McMillan 1968). Some workers also attribute a variety of lesser symptoms; abdominal pains, borborygmi, flatulence and distension, to vagal section (Griffiths 1960).

Selective Vagotomy

The search for a more physiological and less destructive operation which might avoid these sequelae, led Jackson, Franksson and Moore independently of each other (1948) to devise a method of dividing only gastric vagal nerves while preserving the para-sympathetic supply to the remaining foregut and mid-gut and their appendages such as liver, biliary tract and pancreas. The new

/operation

operation, now known as selective vagotomy, consisted of preservation of the coeliac division of the posterior vagus. Griffiths and Harkins (1957) described preservation, in addition, of the hepatic division of the anterior vagus; so-called bilateral selective vagotomy. These workers provided important experimental support for the operation when they demonstrated in dogs that satisfactory gastric denervation, as measured by insulin stimulation, could be achieved by selective vagotomy.

Initial reports by several groups suggest that this is a promising operation. (Griffiths and Harkins 1957, Kraft and Fry 1963; Farris and Smith 1963; Hyde and Hull 1965; Tanner 1965; Amdrup, Clemmesen and Andreassen 1966; Hedensted and Lundquist 1966; Frohn, Desai and Burge 1968). Three groups have attempted assessment by controlled trial. While results appear to show selective vagotomy in a favourable light, especially in respect of completeness of vagotomy, numbers are small (Sawyers, Scott, Edwards, Shull and Law, 1968; Mason, Giles, Graham, Clark and Goligher, 1968; Kennedy and Connell, 1969). The need for further controlled studies has been stressed in a recent comprehensive review of the subject of vagotomy (Kay, 1968). The institution and some technical aspects of such a trial will be described in Part IV, Chapter 23, of this thesis. The clinical data consists of secretory studies and clinical follow-up of a large number of gastric surgical patients, some of whom underwent vagotomy as many

/as

as 20 years ago, although the majority were treated within the past decade. By its very nature such a study will not be complete for another 10 years or more. It is therefore presented as a 'progress report' of a continuing study.

Vagal Anatomy

Before introducing the studies on gastric secretion it is cogent to account for the large anatomical component of this work. The reasons are twofold. Firstly a reassessment of vagal anatomy has been carried out as a basis for the new operation of selective vagotomy. When selective vagotomy was introduced to the Gastro-Intestinal Unit, Western General Hospital, in 1962 it was decided that our knowledge of the distribution of the vagus nerves below the diaphragm was insufficient. An anatomical study upon cadaver specimens was therefore undertaken by the author and this is described in Part I, Chapter 2. It is supplemented by an account of the surgical anatomy observed in our first 145 cases of selective vagotomy (Part I, Chapter 3). The evolution of the operative technique in the light of our anatomical knowledge is reviewed.

The second reason for an anatomical study pertains to 'completeness' of vagotomy.

Completeness of Vagotomy

Of great practical importance common to both truncal and selective vagotomy is the question of completeness of gastric denervation. It is almost unknown for peptic ulcer to recur in the

/presence

presence of complete vagotomy (Kay 1967). Yet in most series of vagotomy with drainage, where there is careful clinical follow-up, there is an incidence of recurrent ulcer ranging from 2 - 10% (Pollock 1952; Tanner 1966; Lynwood-Herrington 1967; Whittaker, Judd and Stauffer 1967; Evans, Zajtchuk and Menguy 1967). It should be noted that even a 10 year follow-up (and most published accounts fall very far short of this) will not reap the full harvest of recurrent ulcers, (Chapter 17, p. 194).

Even more difficult to determine is the true incidence of incomplete vagotomy. An average of 30% is widely accepted (Kay 1967). When one considers that the authors of accounts of follow-up are those especially interested and specialised in the problems of vagotomy one must conclude that this figure is a conservative estimate. Furthermore it will be shown that the general application of the insulin secretion test and its interpretation remain, more than 20 years after its introduction (Hollander 1948), highly debatable, again erring in the direction of underestimation (Part III). A reliable test is crucial to the elucidation of problems arising after peptic ulcer surgery. A large part of the studies described in Parts II, III and IV of this thesis is devoted to efforts to place the performance and interpretation of this test upon a more rational and reliable footing.

Finally, in the history of vagotomy, the wheel may be coming full circle. We have recently developed renewed interest in the

/operation

operation of vagotomy applied without drainage or resection (Burge 1968); no longer truncal vagotomy whose unsuitability for this is established, but selective vagotomy applied as a sole procedure in patients carefully selected on the basis of pre-operative gastric emptying measurements. Such a concept demands effective gastric denervation. The operative technique upon which satisfactory vagotomy depends is outlined in Part I, Chapter 4. In Part IV, Chapter 22, our incidence of incomplete vagotomy, the factors which influence this incidence and the steps necessary to reduce it are analysed. If the studies outlined in this thesis result in more effective post-operative assessment together with a lowered incidence of incomplete vagotomy then its main objects will have been fulfilled.

CHAPTER 1THE HISTORY OF STUDIES OF VAGAL ANATOMY

It is generally acknowledged that the philosophy of modern medicine, based as it is upon the careful study of basic sciences sprang from the teaching of Galen (130-200 A.D.). He himself would have acknowledged a debt to Hippocrates (5th-4th Century B.C.), and to the empiricists Herophilus and Erasistratus of the Alexandrine School of Anatomy and Medicine (3rd Century B.C.).

Galen's contributions to neuro-anatomy represent perhaps his greatest work. Aristotle had maintained that nerves arose from the heart. Galen demonstrated that they originated in the brain and cord. He distinguished only 7 pairs of cranial nerves; those which are now numbered 2, 3, 5, 7, 8, (9, 10, 11) and 12. The sixth pair were the 'wandering nerves' or par vagum.

With the death of Galen the tradition of biological learning in Europe was completely broken. In the eleventh and twelfth centuries the translation of Greek-Arabic texts into Latin brought about a partial revival, and inaugurated the reign of dogma known as the Scholastic Period which was characterised by the pious and unreasoning acceptance of Aristotle and Galen (F. J. Cole, 1944).

Thus it is that descriptions of the vagal anatomy in the earliest printed European textbooks, although fascinating, are

/derived

derived directly from the Corpus Galenicum:-

"It hath very conspicuous and notable nerves from the sixt pair, which at his orificies or mouths are double, disseminated from those branches which make the recurrent nerves and yield certain tendrilles to the lungs and pericardium, or purse of the heart, which tendrilles, because of their softness and the length of their way, are covered over with strong membranes, and do cross one another, that for greater security they might pass obliquely or aside-long; and piercing through the diaphragm or midriffe are on both sides doubly divided, so that the left compasseth the right and back part of the stomack, and the right the left and forepart, which orifice they do involve, that it seemeth to be made altogether of sinewes; from the abundance of which it hath most exquisite sense to stir up and awake the sense of want of nourishment.

"These branches of nerves going downward make his membranes which were only membranous before, to become nervous, being disseminated even to his bottom. These do also improve the nourishing force or faculty of the fleshy fibres of the stomacke. From the left nerve there runneth a branch along the uppermost seat of the stomacke to the pylorus, which when it hath soulded with a few small surcles it goeth thence to the hollow of the liver.

"Wherefore seeing the stomacke hath obtained so many sinewes, it is no wonder that when the braine be affected, the stomacke also bee disturbed,"

Helkiah Crooke. Doctor of Physick, 1631.

The vagal fibres encompassing the seat of the soul (cardia) are clearly shown in early lithographs from the Anatomia of Bartholinus (1651) (Fig. I, 1 & 2).

The/

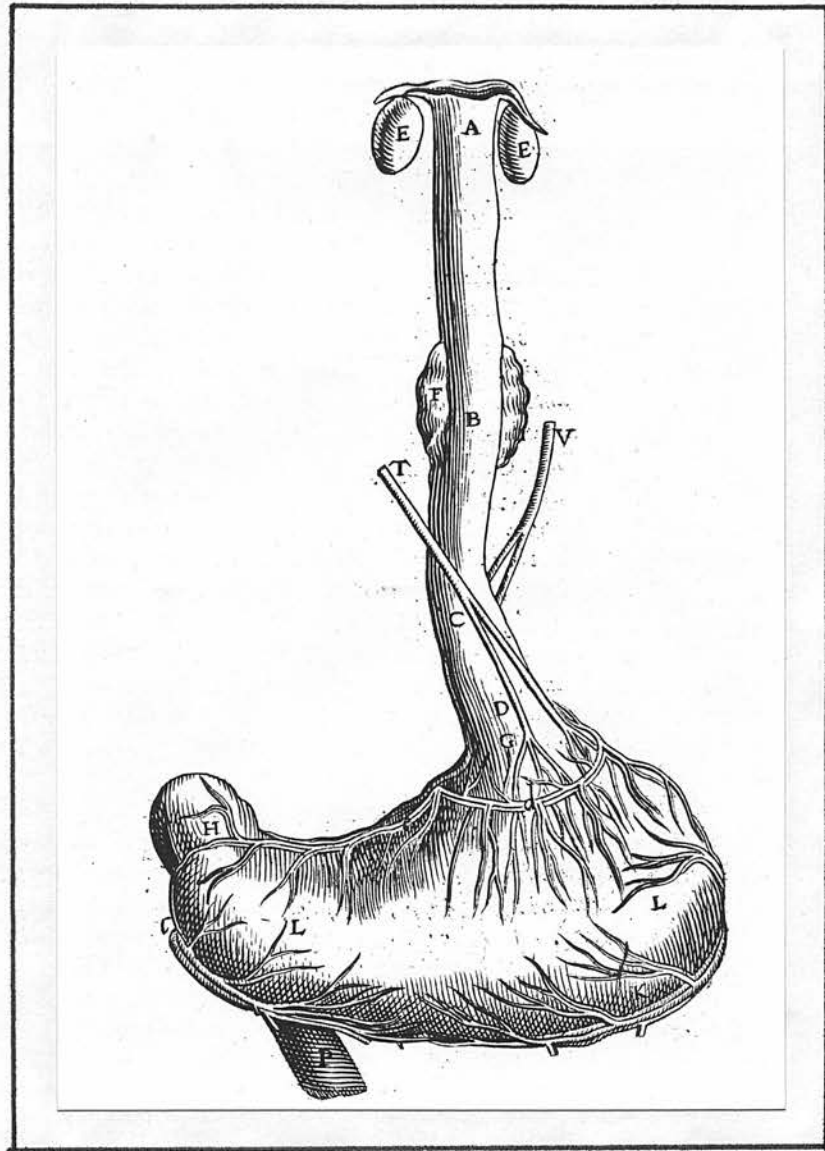


FIGURE I, 1.

Anterior view of oesophagus and stomach.

The anterior vagus (T) is shown as dividing into two upon the lower oesophagus.

From the 'Anatomia' of Thomas Bartholinus;
Leyden. 1640. Ch. 9, p 43.

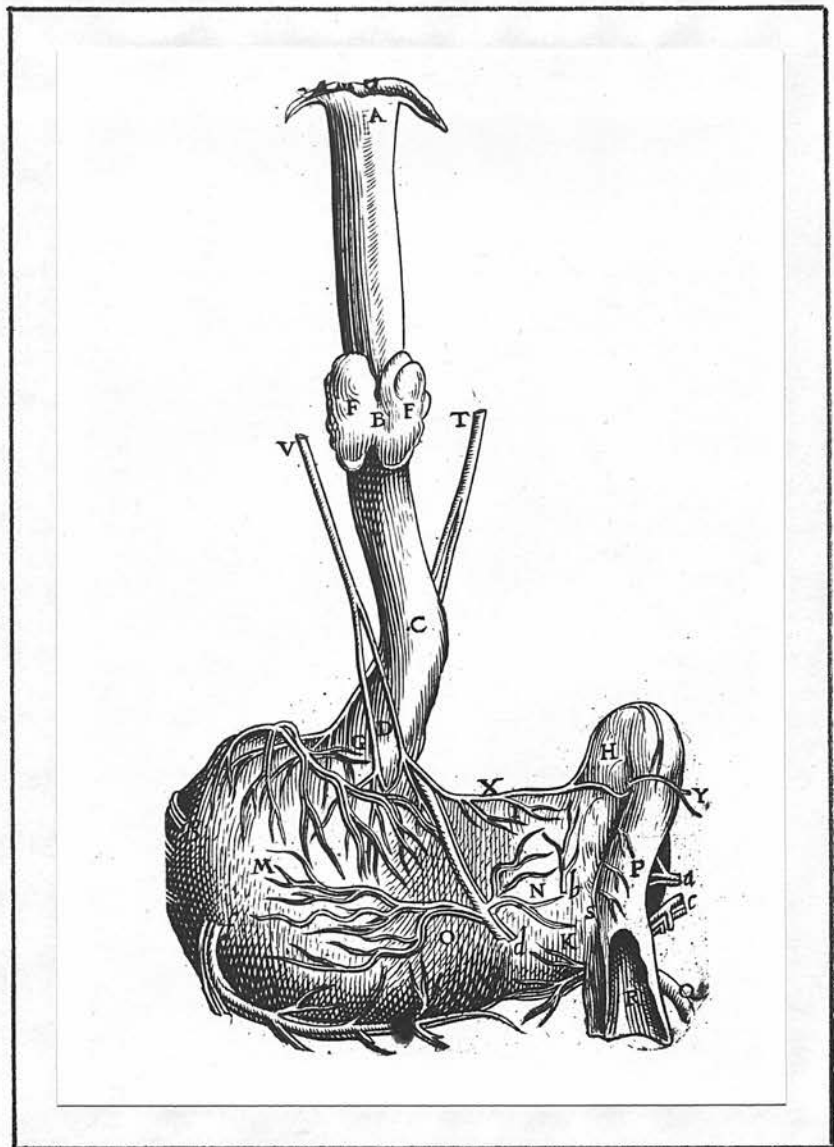


FIGURE I, 2.

Posterior aspect of oesophagus and stomach.

The posterior vagus (V) is shown dividing, like the anterior, into two trunks upon the lower oesophagus. Note the branch (X) coursing along the lesser curveture to the first and second parts of the duodenum.

From the 'Anatomia' of Thomas Bartholinus,
Leyden. 1640. Ch. 9, p 45.

The main anterior and posterior trunks are depicted as dividing a considerable distance above the stomach. The posterior trunk is shown as supplying the distal stomach and also duodenum while the anterior appears only to reach the corpus. This is the reverse of Helkiah Crooke's description quoted earlier which also mentions a distribution of the anterior or left vagus to the liver.

The eighteenth century saw the vagi relegated to the eighth pair. While it was generally agreed that they mainly supplied the stomach there was less certainty as to their subsequent course. Cheselden (1795) described communications with the intercostal nerves below the diaphragm. Portal (1804) commented upon the numerous intercommunicating fibres between the trunks and also described communications with the splanchnic sympathetics. Fyffe (1830) was more precise:-

"The left nerve of the eighth pair gives off nerves to the upper stomach, branches of the gastric plexus to the small curvature, and branches from the right hepatic plexus to the small end of the stomach and the beginning of the duodenum".

Thus the link between the anterior vagus, hepatic plexus and/

and hepato-gastric bundle was recognised. The same author describes the posterior vagus giving branches to coeliac ganglion and to liver.

Nineteenth century texts contained reproductions of many beautiful lithographs of the vagal anatomy. Thus the *Anatomie De L'Homme* by Cloquet (1828) shows a superb illustration of the nerves of the upper abdomen (Fig. I, 3). It is identical with the illustration provided by several authors of the period such as, for example, Knox's translation of the *Tabulae Neurologicae* of Antonio Scarpa (1831). The source of the original engraving (copied by Mitchell in Knox's translation) is not clear.

Detail from this lithograph (Fig. I, 4) shows the anterior vagus (arrowed) amongst a bewildering array of nerve fibres. Although a number of fibres are shown accompanying a very large vessel passing from the left gastric artery to the liver no clearly defined hepatic branches from anterior vagus are visible. It is unlikely that dissections can have been performed in this degree of detail and credit must be given more to the quality of the lithography than to the anatomical accuracy.

Posterior vagus is equally beautifully depicted. A figure from Scarpa (Fig. I, 5) shows the stomach reflected forwards. It may be noted that the posterior vagus (arrowed) is correctly shown as lying separate from the oesophagus while the anterior vagus/

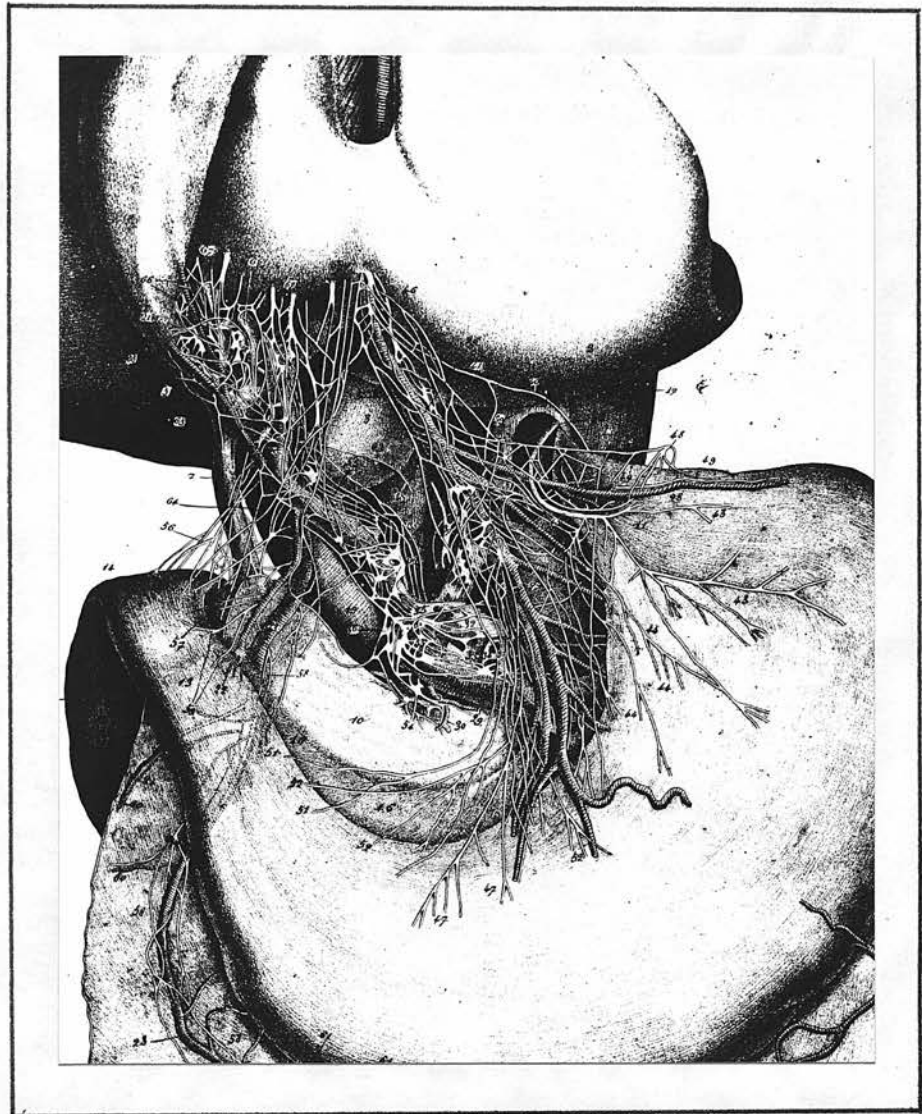


FIGURE I, 3.

A dissection of the autonomic nerves of the upper abdomen.

From 'Anatomie de l'Homme
by Jules Cloquet;
Engelmann; Paris; 1828.
Volume III, pl: CLXXVIII.

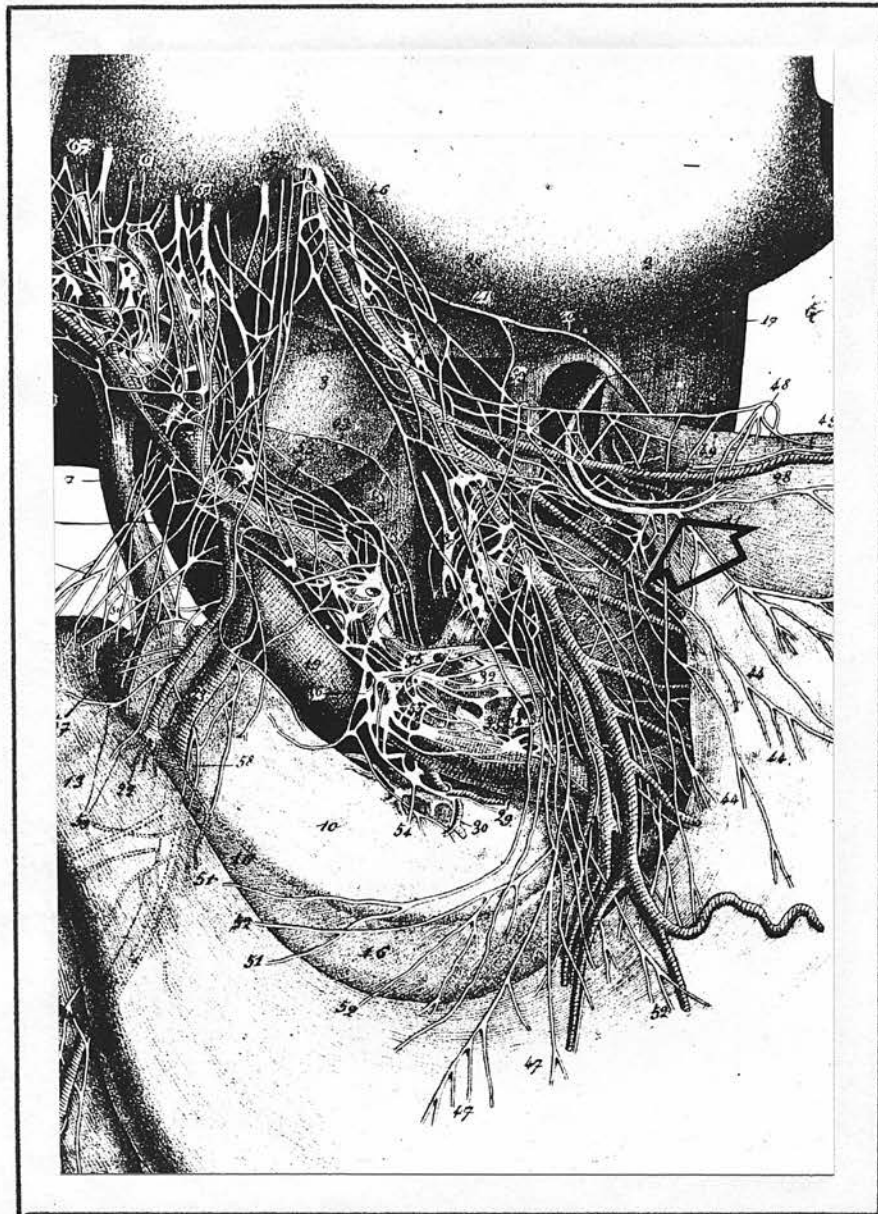


FIGURE I, 4.

Detail from Fig: 1, 3.

Anterior vagus (arrowed) is shown dividing into several gastric branches (44) and contributing to a reticulum of nerves which accompany an abnormal branch of the left gastric artery to the porta hepatis.

Jules Cloquet, 1828.

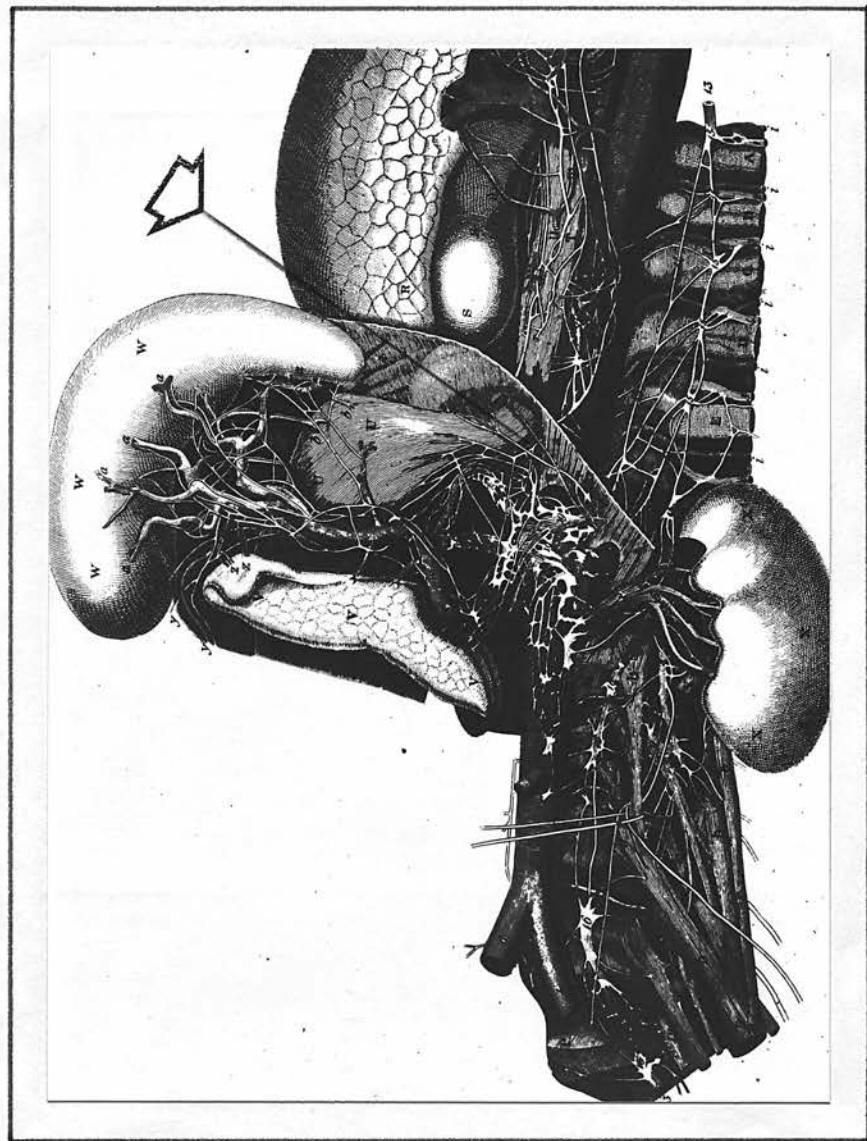


FIGURE I, 5.

Dissection showing the stomach, spleen and pancreas reflected anteriorly.

From: Translation of the 'Tabulae Neurologicae' of Antonio Scarpa, by Robert Knox. Engravings copied from the original by Edward Mitchell. Maclachlan and Stewart, Edinburgh 1831, Pl IX.

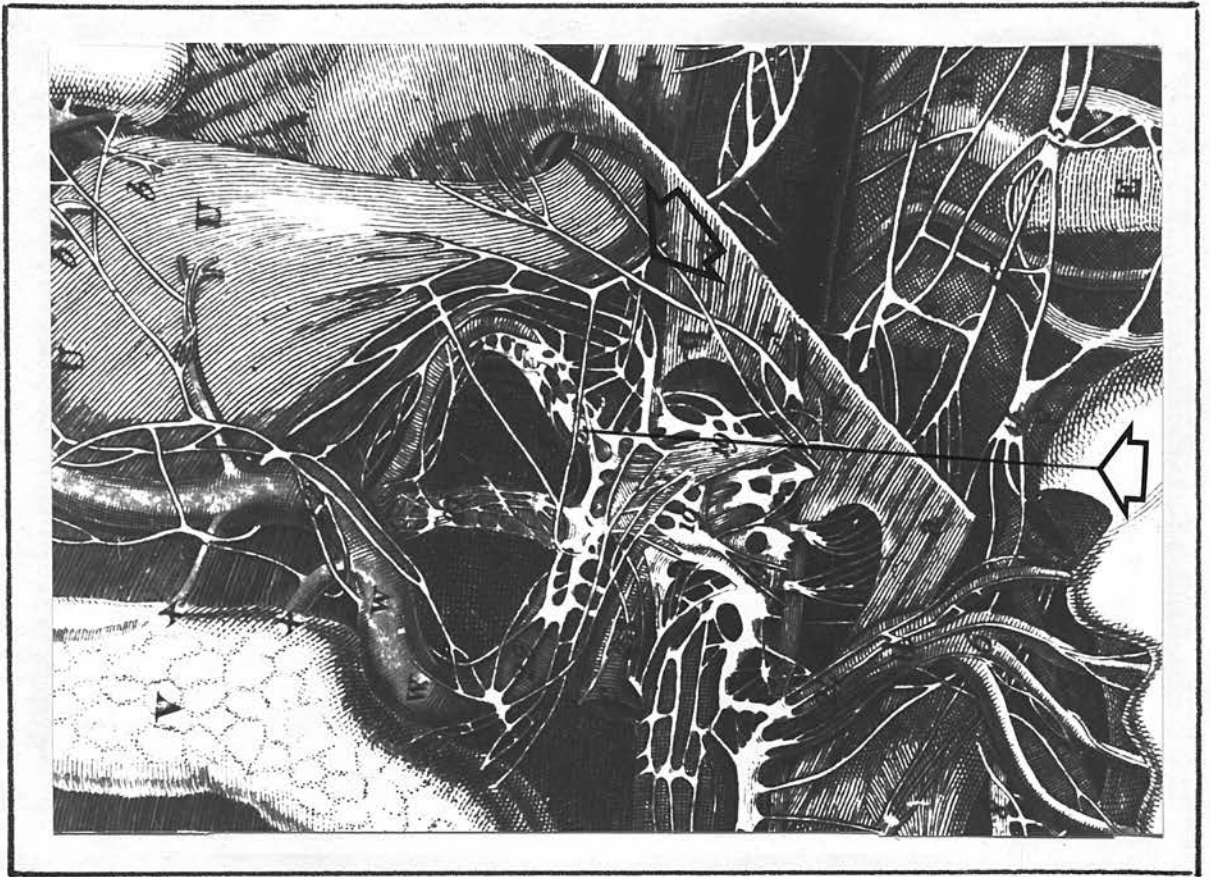


FIGURE I, 6.

Detail from Fig. I, 5. Posterior vagus (arrowed) is clearly shown as a single trunk, giving branches both to the stomach and to the coeliac plexus.

Scarpa: trans. Knox. 1831.

vagus is closely applied to the oesophageal muscle. Detailed examination (Fig. I, 6) appears to show a branch (arrowed) passing from the posterior vagus to the coeliac plexus. Again however there is evidence of artistic licence.

Joseph Swan (1834) made a useful contribution to the knowledge of vagal anatomy. Features of his elegantly illustrated description (Fig. I, 7) are multiple anterior vagal fibres and the hepatic branches shown passing to the hilum. Despite an impression of greater anatomical validity the influence of earlier anatomists is visible in the excess of detail. His illustration of the structures of the posterior abdominal wall (Fig. I, 8) emphasises the large coeliac portion of the posterior vagus (arrowed).

The finest 19th century illustrations of vagal anatomy appear to be those of Bourguery (1839). His lithographs are remarkable for their quality and accuracy. Unencumbered by unnecessary detail his illustration of anterior vagus emphasises multiple anterior trunks and clearly depicts hepatic branches (Fig. I, 9). An unusual view of posterior aspect of the stomach is shown in Fig. I, 10. The anatomical relationships are most accurately shown. The aorta has been excised leaving the branches of the coeliac axis and the dense coeliac ganglion (arrowed). Detail from the preceding figure (Fig. I, 11) shows the major part of the posterior vagus (arrowed) passing to the coeliac plexus and underlines/

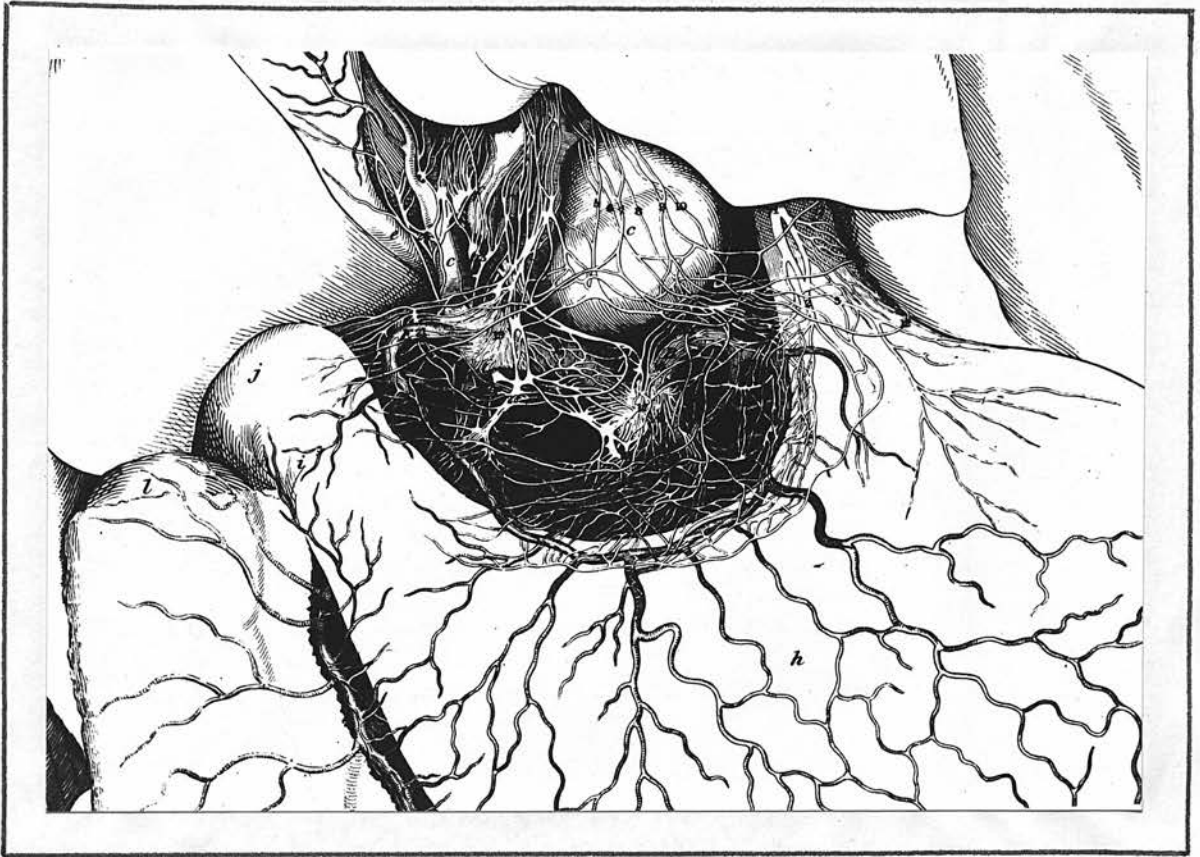


FIGURE I, 7.

Anterior aspect of the stomach. A double anterior trunk (1) is shown re-uniting (2) near the cardia. The nerve appears to be supplying branches to oesophagus, stomach (3), coeliac and hepatic plexuses. Note that the nerves of the lesser curvature are correctly shown as ending short of the pylorus.

From: 'A demonstration of the nerves of the human body'. Joseph Swann. Longman, Rees.. London. 1834. Pl VII.



FIGURE I, 8.

The posterior aspect of the stomach, spleen and pancreas. The posterior vagus (A) passes to the coeliac ganglion (2). Gastric branches are small and few.

Joseph Swann. 1834. Pl VI.

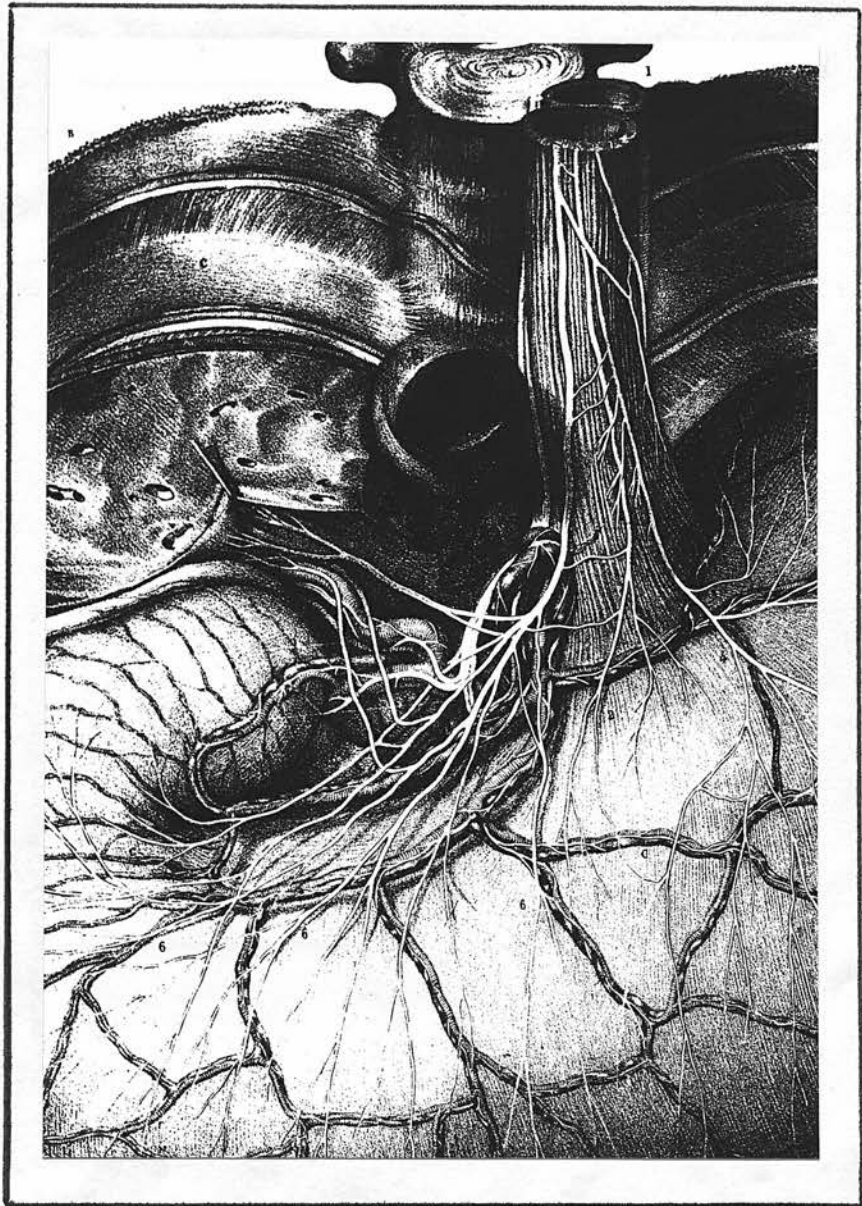


FIGURE I, 9.

A dissection of the nerves of the oesophagus and stomach. Note the multiplicity of anterior vagal fibres on the lower oesophagus and several, widely-spaced hepatic branches. The posterior vagus can also be seen on the left gastric artery.

From: 'L'anatomie de l'homme' by J.M.Bourgery.
Lithography by N.H.Jacob. Jules Didot.
Paris, 1839, Vol. 5., Pl 22.

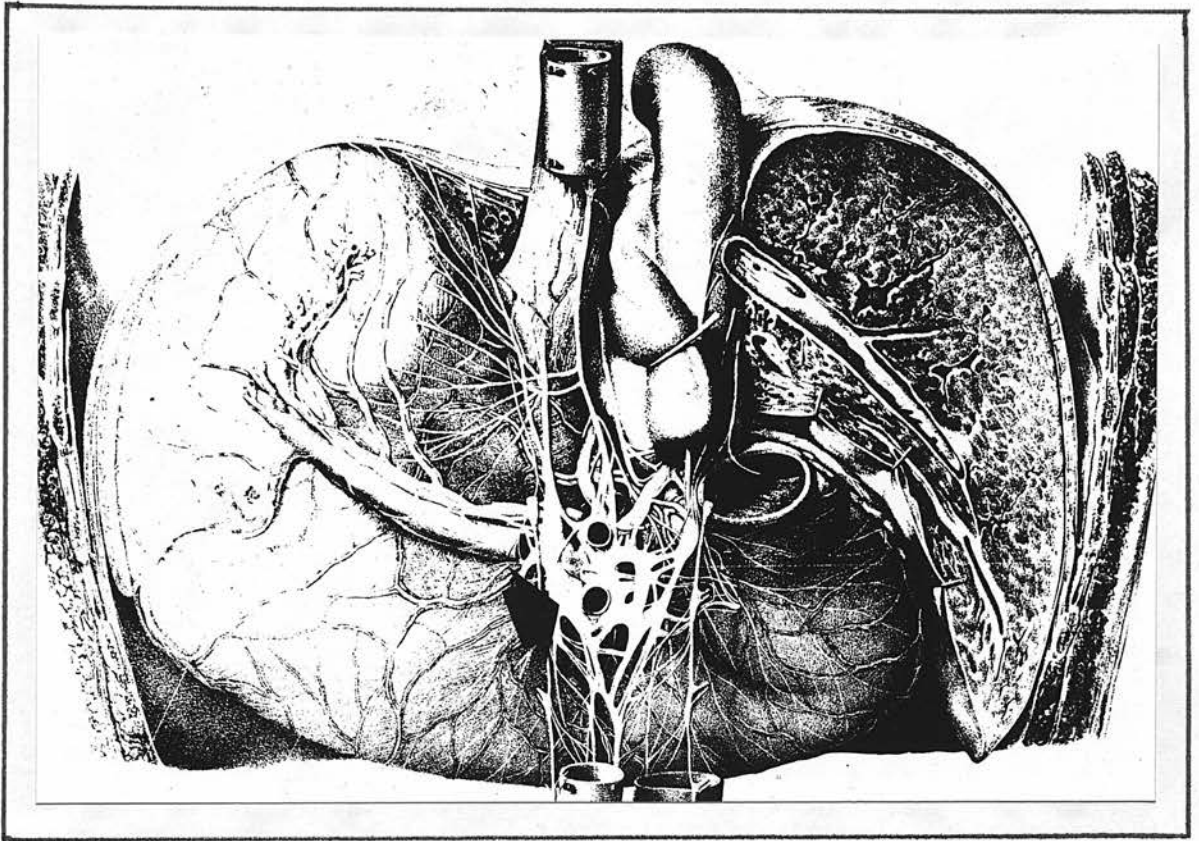


FIGURE I, 10.

Posterior approach to the coeliac plexus (arrowed) and related nerves.

J.M.Bourgery, 1839, Pl 23.

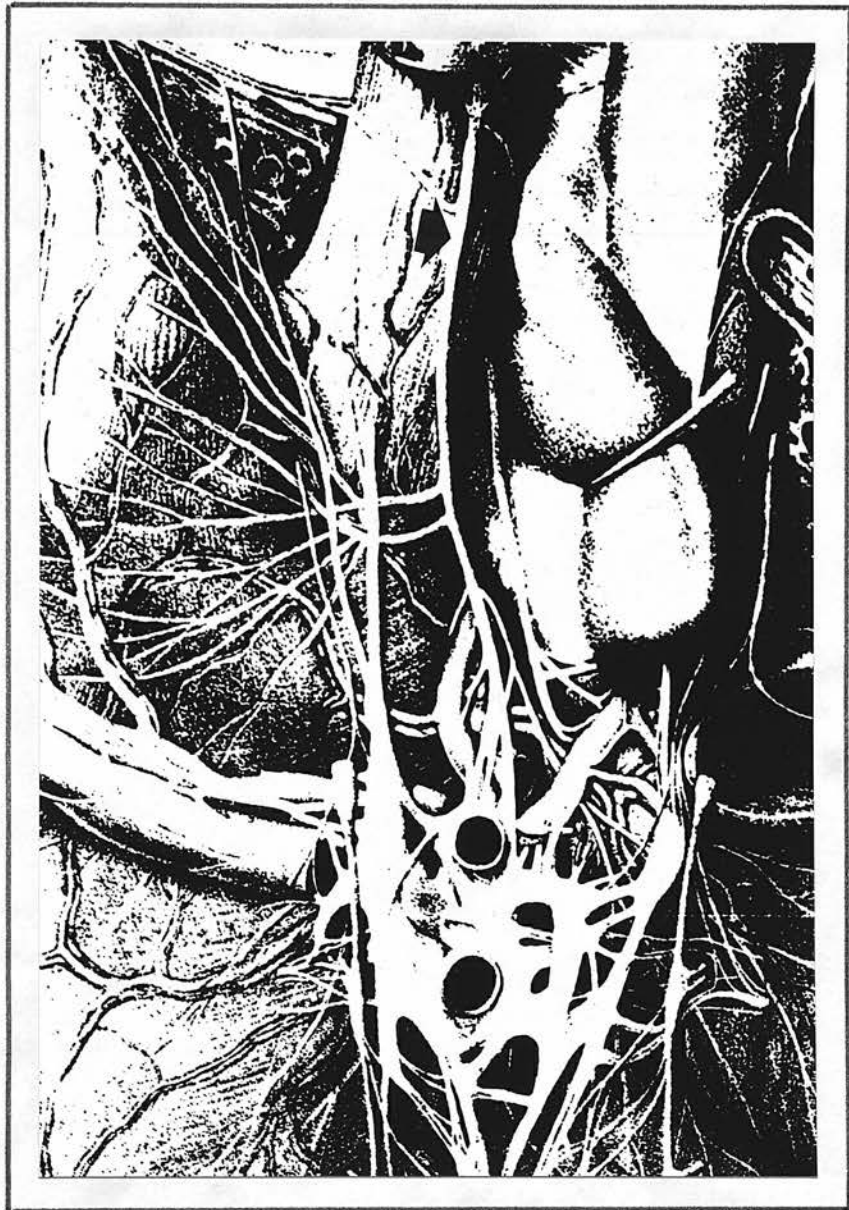


FIGURE I, 11.

Detail from Fig. I, 10. The posterior vagus (arrowed) passes to the coeliac plexus. It is depicted as supplying only two main gastric branches.

J.M.Bourgery. 1839. Pl 23.

underlines the close relationship of the nerve with the left gastric artery.

An illustration taken from the studies of John Lizars (new edition Edinburgh 1856) demonstrates the hepatic branches of the anterior vagus and also shows the nerve of the lesser curvature later known as the nerve of Latarjet (Fig. I, 12).

Thus the anatomical foundations were soundly laid for the 20th century gastric surgeon. Little is to be gained by enumerating more recent descriptions. Certain contributions should however be acknowledged. Latarjet (1922) provided a careful description of the subdivisions of the vagal trunks. In particular he described the hepato-gastric pedicle and the long nerves of the lesser curvature to which his name has been applied.

McCrea (1924) was the first to demonstrate, by a series of dissections, that the vagal anatomy in this area was subject to variations. He defined more precisely than hitherto the courses of the vagal divisions and their connections with the sympathetic system. The introduction of truncal vagotomy brought a spate of papers analysing vagal variations (Miller and Davies 1947; Bradley, Small, Wilson and Walters 1947; Chamberlin and Winship 1947). Since the major debate at that time concerned the relative merits of transthoracic versus transabdominal vagotomy these authors studied the nerves at the level of the lower gullet.

Selective vagotomy brought with it a further series of studies, /

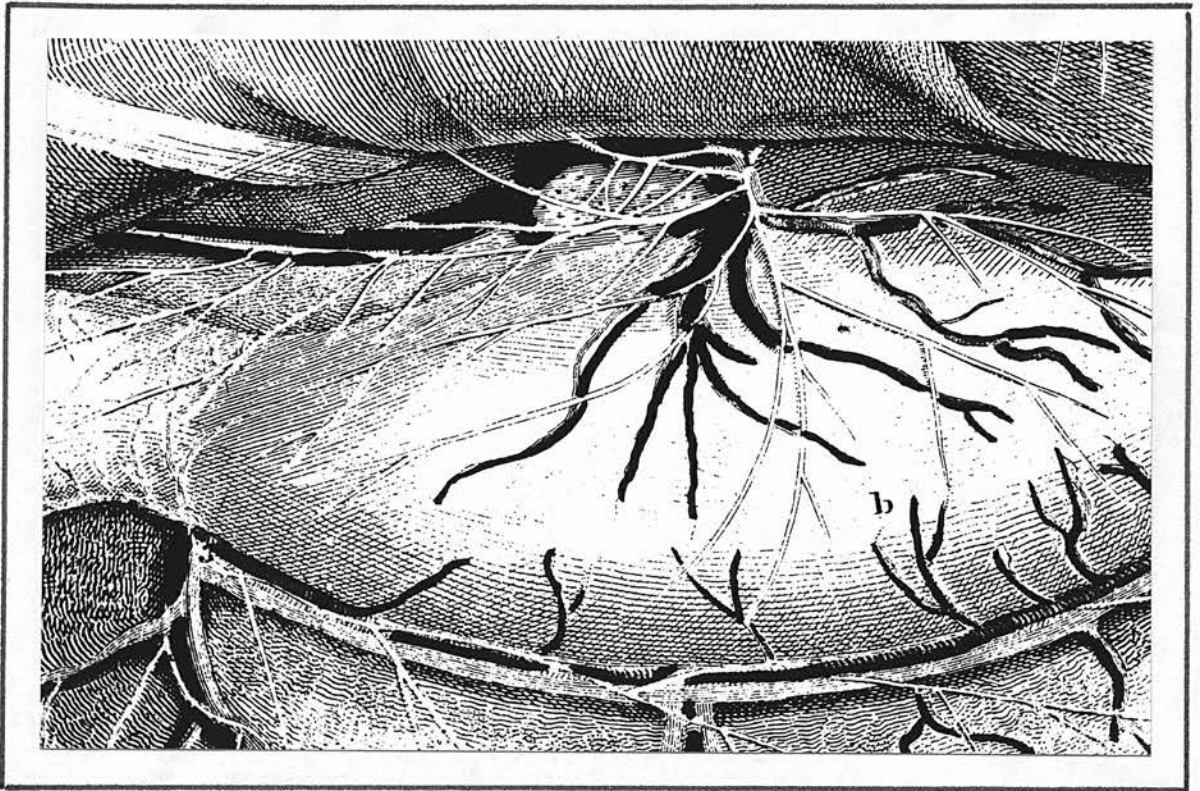


FIGURE I, 12.

A dissection of the anterior vagus. It is shown as a single trunk. Several widely-spaced hepatic branches are depicted.

From: 'A system of anatomical plates of the human body'. John Lizars. Edinburgh. 1856. Pl IX.

studies, including the one described in this thesis. An excellent early study in this group was that of Jackson (1948). Particularly important was his analysis of the variable relationship between the coeliac division of the posterior vagus and the left gastric artery.

Despite a wealth of anatomical studies little is known about the distal course of non-gastric vagal fibres. The reason for this is the difficulty of tracing nerves through the hepatic and coeliac plexuses. Physiological animal experiments have consisted of observing changes in function in response to electrical or other stimuli. Although Iggo (1967) has isolated and stimulated individual afferent and efferent vagal fibres, the majority of studies have involved stimulation of mixed bundles of afferent and efferent nerves subserving multiple functions. Evans and Murray (1954) demonstrated that vagal nerves entering the abdomen of the rabbit comprised approximately 26,000 individual fibres. In man the number varies between 16,000 and 101,000 with a mean of 57,000. (Hoffmann and Schnitzlein 1961). Most authors agree that more than 90% are myelinated and that approximately 90% are afferent. The latter belief has been strongly challenged by Keen (1966) and remains to be elucidated. Vagal efferents in the main nerves are preganglionic. Much remains to be learnt about their intramural connections and about the relationship between post-ganglionic nerve end-organs and the structures such as digestive glands which they activate. Many gastric physiologists believe that some vagal effects/

effects such as exocrine secretion are achieved indirectly by vasomotor control rather than direct innervation of secreting cells (Jacobson 1965).

Fortunately, although our grasp of the cellular anatomy is incomplete, as surgeons we may still refine our techniques by studying the grosser structures.

CHAPTER 2DISSECTIONS OF VAGAL ANATOMYIN THE CADAVER

When selective vagotomy was instituted at the Gastro-Intestinal and General Surgical Units, Western General Hospital, in 1962, a preliminary anatomical study was performed upon cadaver material.

METHOD

Blocks of tissue comprising thoracic and abdominal aorta, diaphragm, oesophagus, stomach, duodenum, liver, spleen and pancreas were examined from fresh cadavers. Twelve such blocks were obtained in all. Because dissection is easier on fresh tissue, and because it was preferable to obtain photographs before bleaching by the fixative, each block was dissected as soon as possible after death. Measurements and drawings were taken from the original specimens and from photographs. In the following description the distribution of the abdominal vagi is systematically described. The findings of other authors are included at relevant points at this stage rather than in subsequent discussions to avoid unnecessary duplication of descriptive detail. For the same reason, under each heading, the anatomical review is immediately followed by an analysis of the findings in this cadaver study.

The Normal Pattern:Vagus Nerves Above the Cardia -

Fibres of the vagus nerves destined for the digestive tract emerge/

emerge from the posterior pulmonary plexus on each side to form the oesophageal plexus, a variable reticulum clinging to the oesophageal wall. By the time it has reached the oesophageal hiatus the plexus has become defined into a number of vagal trunks. The majority of the fibres from the right thoracic vagus enter the posterior abdominal vagus, while the majority from the left thoracic vagus become anterior, but there are numerous intercommunicating bundles.

The number of trunks passing through the hiatus has been much discussed in the literature. In half to two-thirds of cases there is a single anterior and single posterior trunk at this level (Mitchell, 1940; Chamberlain and Winship, 1947; Miller and Davies, 1947; Bradley, Small, Wilson and Walters, 1947; Jackson, 1948). The posterior trunk lies to the right of the midline of the oesophagus and is usually separated from it by loose areolar tissue.

When the oesophagus is drawn forward, either during dissection or at operation, the nerve becomes further separated because it is tethered postero-medially by its short and inelastic coeliac division. The anterior nerve is closely applied to the oesophagus and usually slightly to its left side. Mobilisation of the lower oesophagus usually carries the anterior vagus with it. The nerve, being inextensible, indents the oesophagus when the latter is drawn forward or when traction is applied to one of the gastric vagal branches.

The/

The two trunks are linked by a number of long and short communicating strands. In the lower thorax and upper abdomen branches to pericardium, aorta, oesophagus and diaphragm are found. Below the oesophageal hiatus the anatomical arrangement most commonly found in my dissections will be described as 'normal', and in fact agrees with the descriptions by previous authors (McCrea, 1924; Hovelacque, 1927; Mitchell, 1940; Jackson, 1948).

The Anterior Vagus -

In 8 cases in this series the main anterior trunk was single (Fig. I, 13, Case 7). The trunk divides approximately at the level of the oesophago-gastric junction into its two principal divisions; hepatic and gastric. Two very much smaller additional divisions sometimes described are the pyloric and coeliac.

In 4 cases the trunk was double. In 1 of the 4 the two divisions remained separate (Fig. I, 14, Case 5) and in 3 they reunited below the hiatus before their terminal branching (Fig. I, 15, Case 9). In Case 1 the terminal division was abnormally high occurring at the level of the hiatus. Jackson (1948) has reported a case where the hepatic branch was seen to arise in the thorax.

The Hepatic Branches -

This bundle of fibres passes to the right between the two layers of the lesser omentum and can be seen in all but the very obese subject, outlined against the caudate lobe of the liver (Fig./

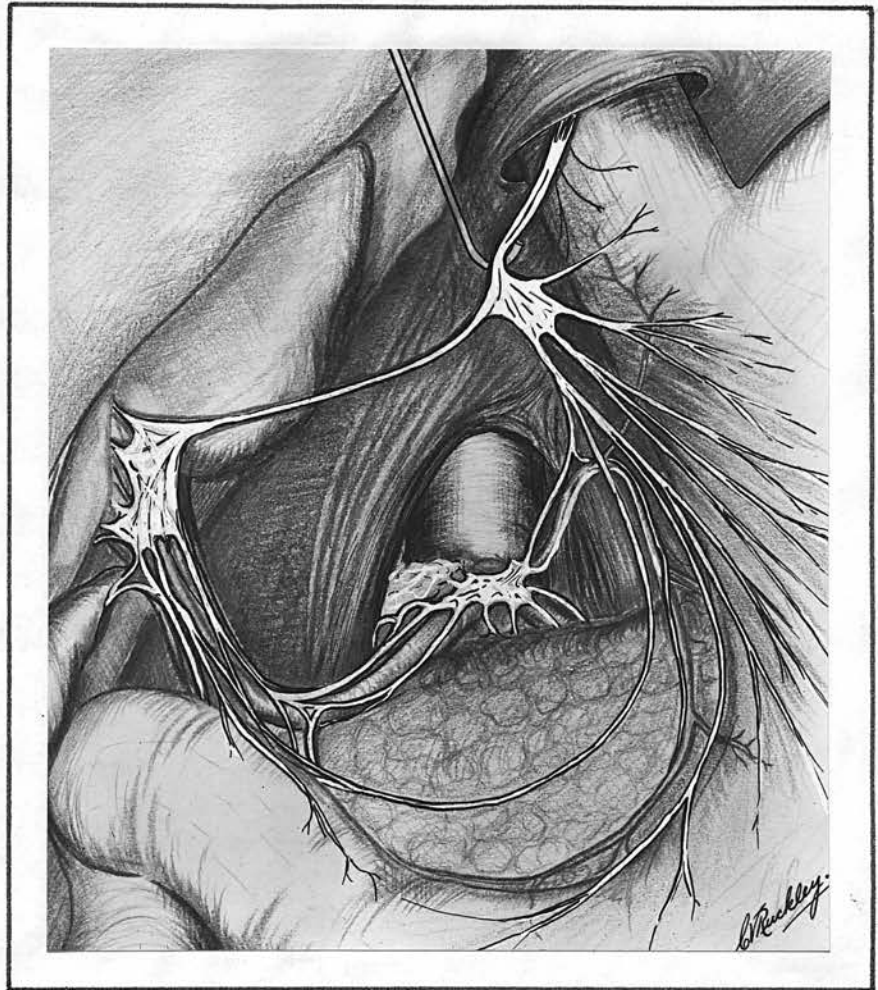


FIGURE I, 13; CASE 7.

Normal anterior vagus. The single main trunk has been picked up with a nerve-hook and drawn to the right. The principal nerve of the lesser curvature (the nerve of Latarjet) can be seen outlined anterior to the pancreas.

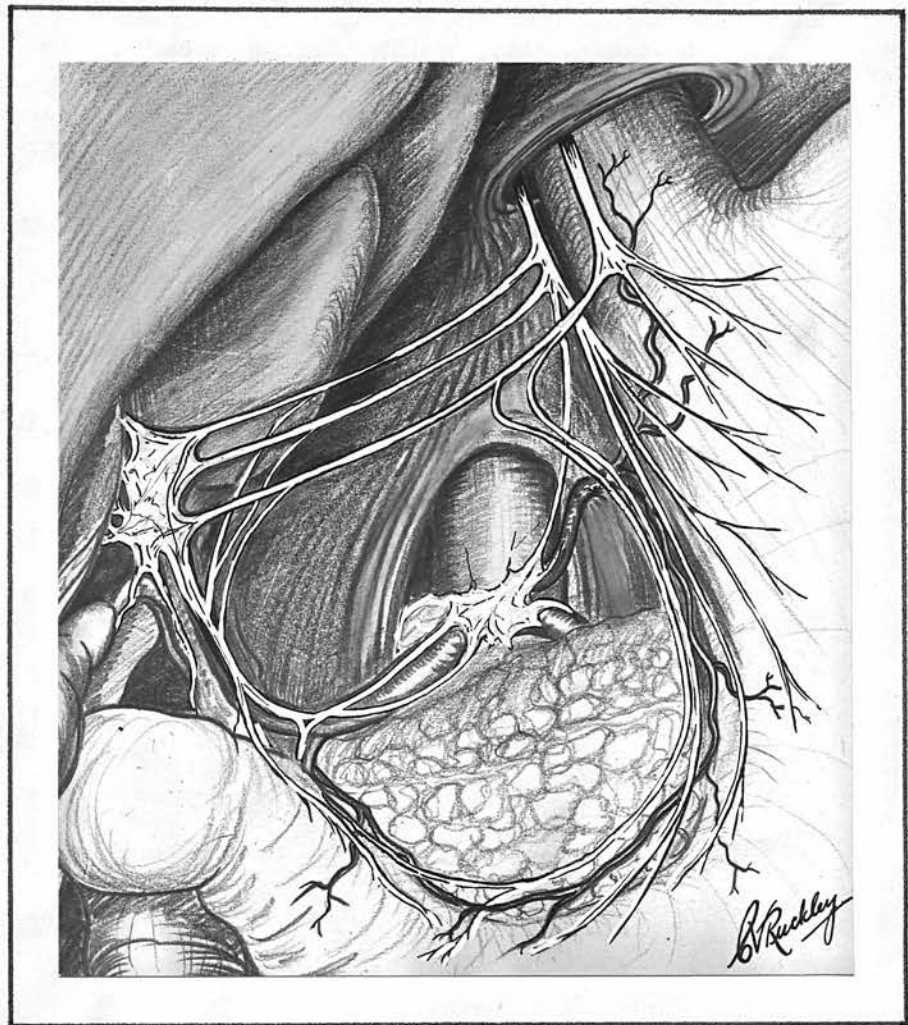


FIGURE I, 14, CASE 5.

Separate anterior vagus nerves, each supplying
hepatic branches.

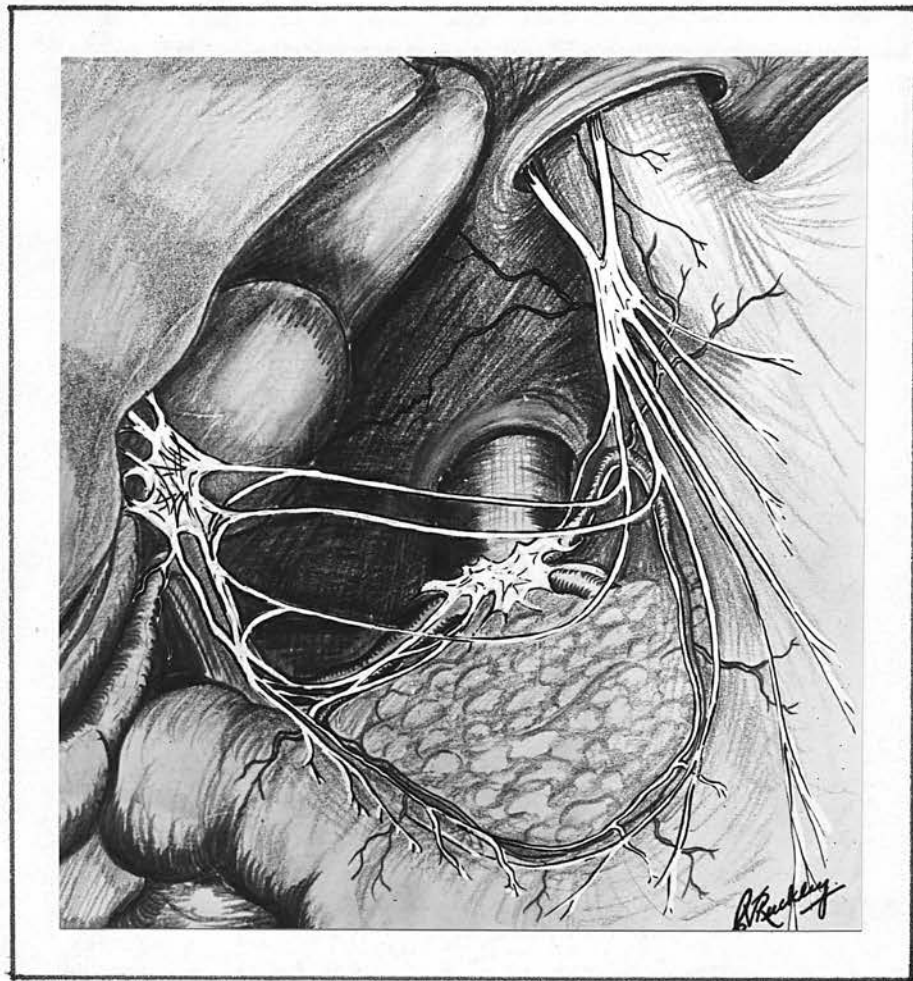


FIGURE I, 15. CASE 9.

Separate anterior trunks uniting at the cardia.
The hepatic branches are unusually low and widely spaced.

(Fig. I, 16, arrowed). In and alongside the fissure for the ligamentum venosum lies the hepatic plexus of autonomic nerves. Twigs from the hepatic division can be followed through the plexus into the liver, to the biliary apparatus and descending in the hepato-gastric ligament to the coeliac plexus, pyloric antrum, pylorus, proximal parts of duodenum and pancreas.

In 4 cases the hepatic division was a single bundle, in 4 there were two main divisions and in the remaining 4 three or more separate bundles. These branches may run across the omentum as much as 2 cm. or more apart, the lowest fibres often arising in common with the pyloric branch of the principal anterior nerve of the lesser curvature (Fig. I, 17, Case 1), its origin then being unusually low. It may be difficult to decide whether such a branch should properly be named "hepatic" or "pyloric". The importance of this finding to the surgeon seeking satisfactory selective vagotomy will be dealt with in the section on operative technique.

As previous authors have noted (Burge, Rizk, Tompkin, Barth, Hutchison, Longland, McLennan and Miln, 1961), separate hepatic branches may arise from separate anterior trunks (Fig. I, 14, Case 5)

Where hepatic branches are multiple each can generally be demonstrated to give contributions to the hepato-gastric bundle as well as the hepatic plexus.

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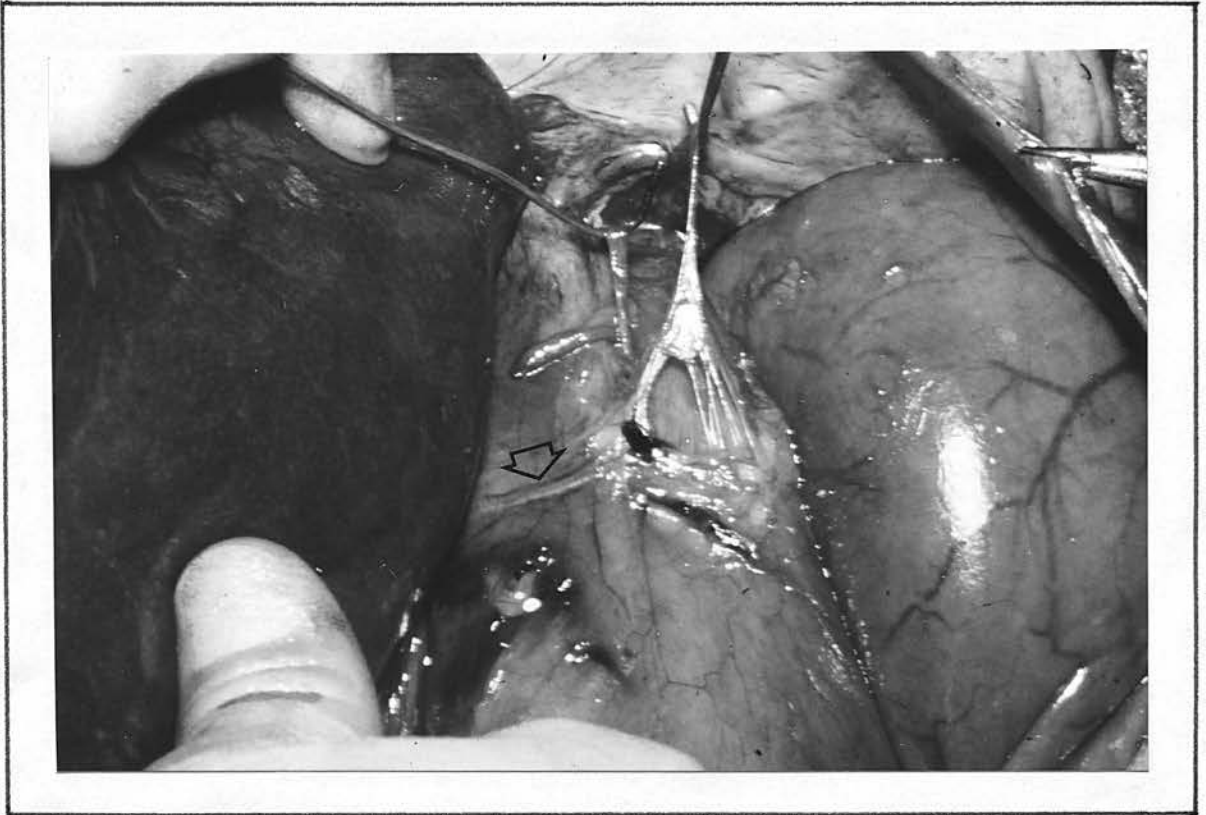


FIGURE I, 16.

A dissection in the cadaver: the peritoneum overlying the cardia has been incised and the main vagal trunks picked up with nerve hooks. Note the multiple fine gastric branches from the anterior vagus and the bulky hepatic division (arrowed) crossing the lesser omentum. The anterior vagus lies towards the left of the anterior surface of the oesophagus while the posterior trunk lies to the right and somewhat separate from the oesophagus posteriorly. The posterior vagus is a much larger nerve than the anterior.

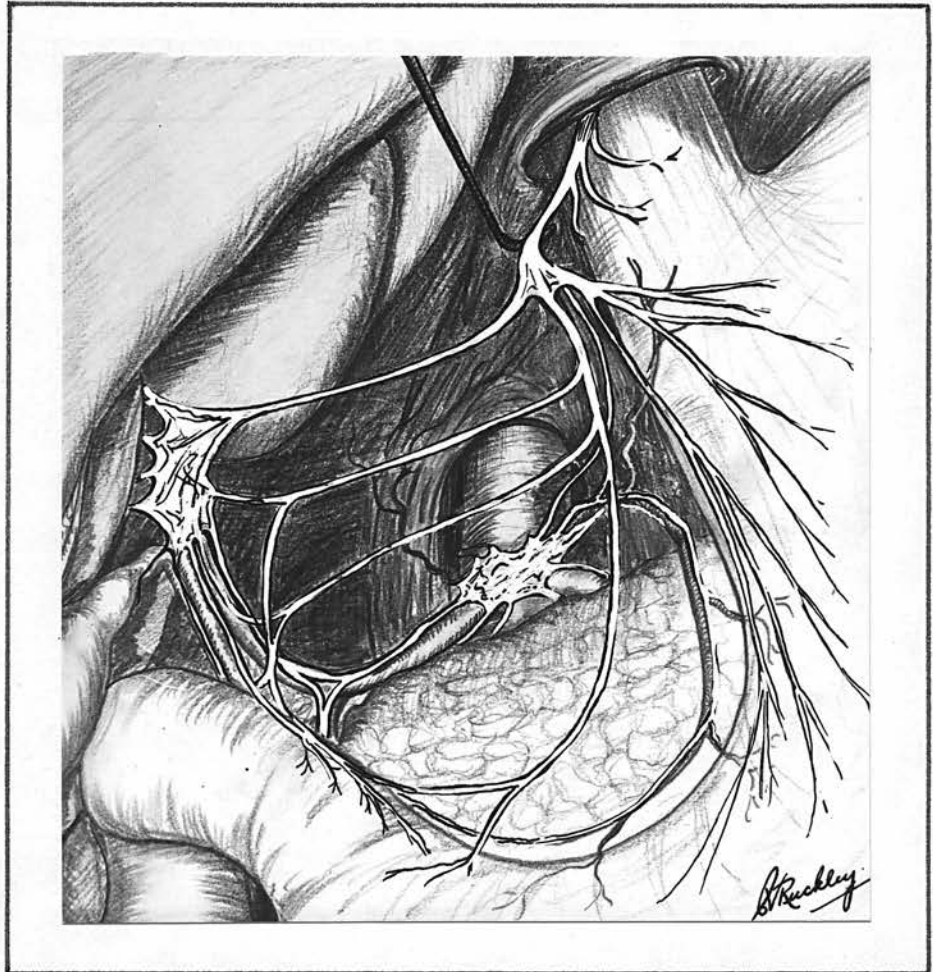


FIGURE I, 17. CASE 1.

The hepatic branches may be widely separate.
A small coeliac branch may arise from the
anterior vagus.

The Gastric Branches -

These may arise separately as 5 - 10 thin twigs or as 1 - 4 main divisions which then subdivide on the anterior surface of the stomach. The majority pierce the serosa about one third of the way across the stomach. Although some authors have described plexuses in the distribution of the gastric branches there were no such plexuses in the sense of intercommunicating fibres seen in the course of these dissections.

The most medial of the gastric branches descends parallel to the lesser curvature, often widely separated from the left gastric artery, to enter the stomach in the region of the incisura. This is "the principal anterior nerve of the lesser curvature" of Latarjet or the "greater anterior gastric nerve" of Mitchell (1940).

In respect of the variations the findings in this series agree with the excellent studies of these branches made by McCrea (1924), Mitchell (1940) and Jackson (1948).

Jackson noted 2 cases out of 50 in which there were no gastric branches from the anterior vagus. No such total absence occurred in this series but in 1 case the anterior vagus was very thin, its main bulk passing to the hepatic plexus while its gastric branches were very scanty, and several twigs were seen to pass from the posterior vagus to the anterior surface of the stomach (Fig. I, 18, Case 6). In several cases the upper gastric branches arose at or above the level of the oesophageal hiatus.

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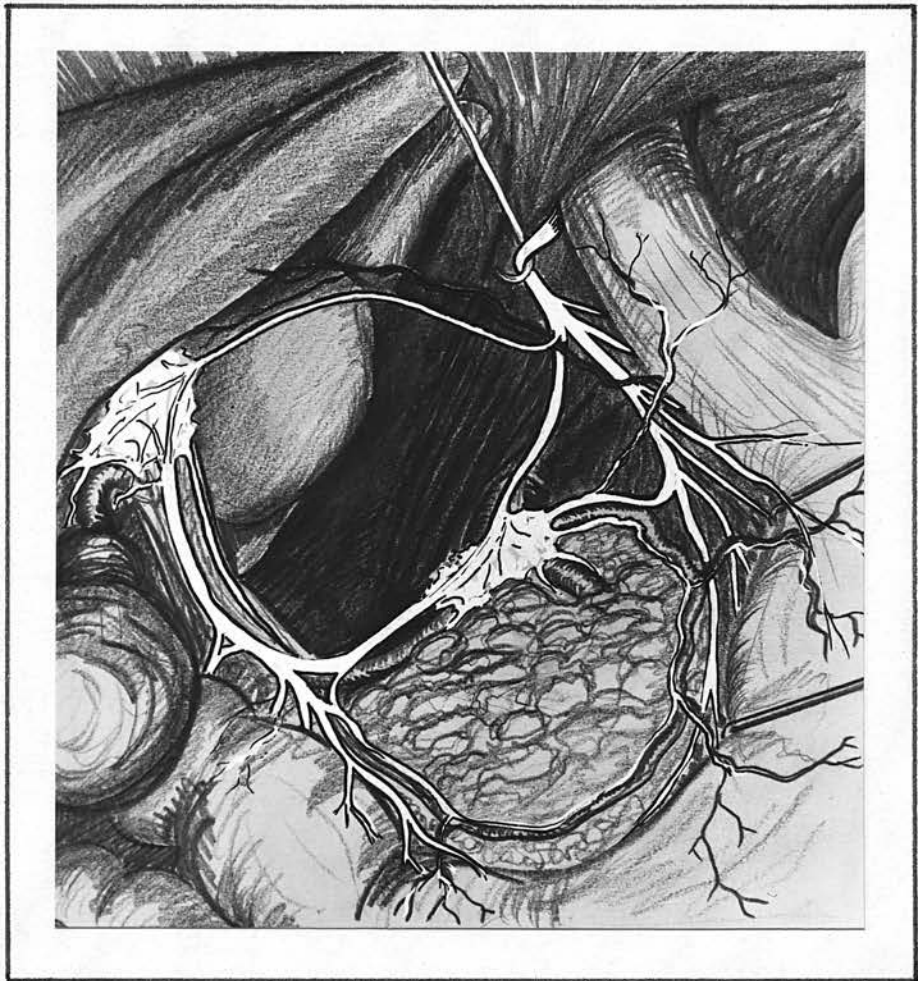


FIGURE I, 18. CASE 6.

The posterior vagus may supply small branches to the anterior surface of the stomach.

The principal anterior nerve of the lesser curvature was present in every case. Traction upon it at the start of a dissection may provide a rapid method of identifying the main anterior trunk which becomes taut and indents the oesophagus. Jackson noted the principal nerve to be present in 56% of cases. It commonly arose from the main trunk in this series in conjunction with the hepatic branches and in 1 case was deviated at its origin approximately 3 - 4 cm. to the right with them (Fig. I, 14, Case 5).

The Pyloric Branch -

This is a fine filament descending between the layers of the lesser omentum parallel to the lesser curvature and dividing to send branches to the hepatic plexus and to pylorus and duodenum. It is commonly absent.

Out of 12 dissections this branch was present in 6, being double in 1 case. It should be admitted however that this slender nerve could not be demonstrated to supply the pylorus, as a number of authors have claimed, owing to the difficulty of tracing it within the hepato-gastric bundle. In half the cases it could not be found and it is probably better to regard this nerve as a variant of the principal nerve of Latarjet.

The Coeliac Branch -

Mitchell (1940) has clearly described fibres destined for the coeliac plexus arising from the anterior vagus. Other authors have/

have generally not included this branch in their descriptions and it is not mentioned in textbooks.

In this series branches from the anterior vagus appeared to pass to the coeliac ganglion by three routes. Firstly the hepato-gastric bundle has a dense connection with the ganglia via the hepatic artery. Secondly fibres could be seen joining the nerves passing to the ganglion along the left gastric artery. Thirdly, in 5 specimens a fine twig was observed to pass from the main trunk, separate from the left gastric artery, directly to the coeliac ganglion (Figs. I, 13 and I, 17). It was concluded however that it would not be practical to seek these fine branches at operation.

The Posterior Vagus - (Fig. I, 19, Case 4)

The anatomy of the posterior vagus is more consistent than that of the anterior. It is very rare for the main nerve-bundle to be other than a single trunk. It is generally larger than the anterior. It divides at approximately the same level as the anterior trunk, i.e. at the level of the oesophago-gastric junction or 1 - 3 cm. postero-superior to the apex of the curve of the left gastric artery.

The main divisions are gastric and coeliac. Fine hepatic branches can sometimes be observed by careful dissection.

It/

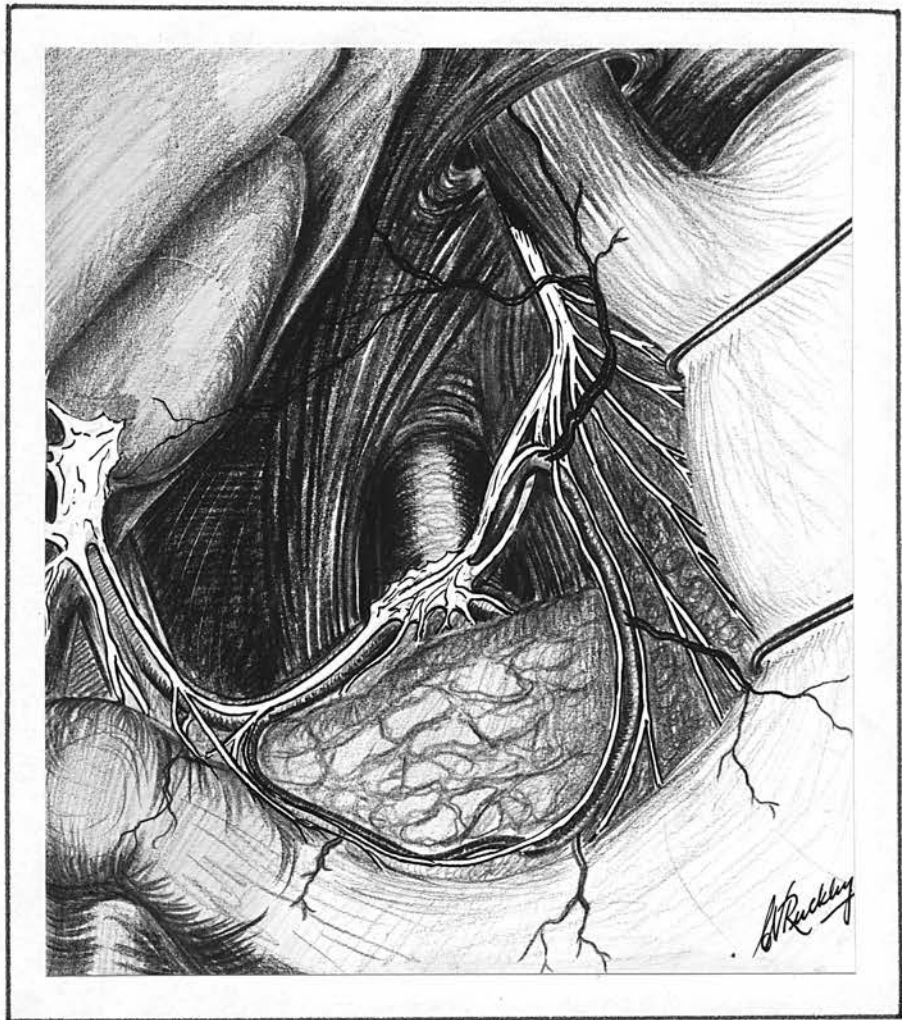


FIGURE I, 19, CASE 4.

Normal posterior Vagus.

It should be stressed that the main portion of the nerve passes on to be distributed via the coeliac ganglion. The gastric nerves represent only a small proportion of its bulk.

In only 1 dissected case was the main trunk double, and even here the two stems joined below the oesophageal hiatus to give the normal branches.

The Hepatic Branch -

This slender division of the posterior trunk is not described by most authors. Nevertheless fibres of the posterior vagus can normally be traced to the hepatic plexus via the left gastric artery, coeliac plexus and hepato-gastric bundle. In 7 specimens there were also fine filaments accompanying the hepatic branch of the left gastric artery. Generally this arterial branch is very fine but in one case a very large left hepatic artery arose from the left gastric, a well recognised arterial anomaly.

The Gastric Branches -

These branches, similar to those of the anterior vagus, may arrive as numerous separate strands up to 10 in number or as 1 - 4 large nerves ramifying on the posterior surface of the stomach. A plexiform arrangement with numerous communicating strands was quite common in the distribution of the posterior gastric nerves, unlike those of the anterior nerves in this series. The principal posterior nerve of the lesser curvature runs close to the left gastric artery or, when the latter divides into two main branches, close/

close to its posterior division. It enters the posterior surface of the stomach in the region of the antrum. As in the case of the anterior nerve it was quite common to find gastric branches arising at the hiatus or above.

In one specimen, as noted earlier the posterior vagus gave branches to the anterior surface of the stomach (Fig. I, 18, Case 6).

The Coeliac Branch -

This represents the main posterior trunk continuing to the coeliac plexus and beyond. It joins the left gastric artery 2 - 4 cm. from the artery's origin and descends along it to the coeliac axis. The pancreas may require to be displaced inferiorly to allow demonstration of its distal course and separation of the nerve from the companion artery may be difficult. The coeliac plexus itself is so dense that it is impossible to trace the majority of the fibres further. Attempts at detailed dissection in this area enable the surgeon to appreciate that the clinical condition of mesenteric angina due to coeliac compression by neuro-fibrous tissue recently described (Snyder, Mahoney and Rob 1967) is a credible possibility.

With the aid of dissecting spectacles or a dissecting microscope many of the fibres can be seen to continue through the coeliac plexus to the superior mesenteric plexus and also forming a thick leash passing along the hepatic artery to be distributed with/

with its branches. Such fibres may be seen to accompany the right gastric artery ascending the lesser curvature but in these dissections they could not be followed more than 2 cm. up the antrum. It should also be pointed out that there is no evidence that these nerves have any secretory function nor indeed that they are parasympathetic.

There is a bundle of nerves visible near the free edge of the lesser omentum, the hepato-gastric bundle. Fibres can be seen directly to join this bundle from the hepatic branches of the anterior vagus. Once again however it cannot be determined by dissection whether the main bulk of these nerves are vagal or sympathetic.

By dissection it was confirmed that the coeliac division comprises the major portion of the posterior vagal trunk joining the left gastric artery 2 - 4 cm. from the vessel's origin in 7 cases. The remainder varied as follows:-

- 1) The coeliac branch arose at the hiatus, descended on the right crus, to reach the coeliac plexus independant of the left gastric artery (Fig. I, 20, Case 11).
- 2) The branch rose with the principal posterior nerve of the lesser curvature, descended close to the stomach to reach the left gastric artery where it turned abruptly to run along the artery to the coeliac/

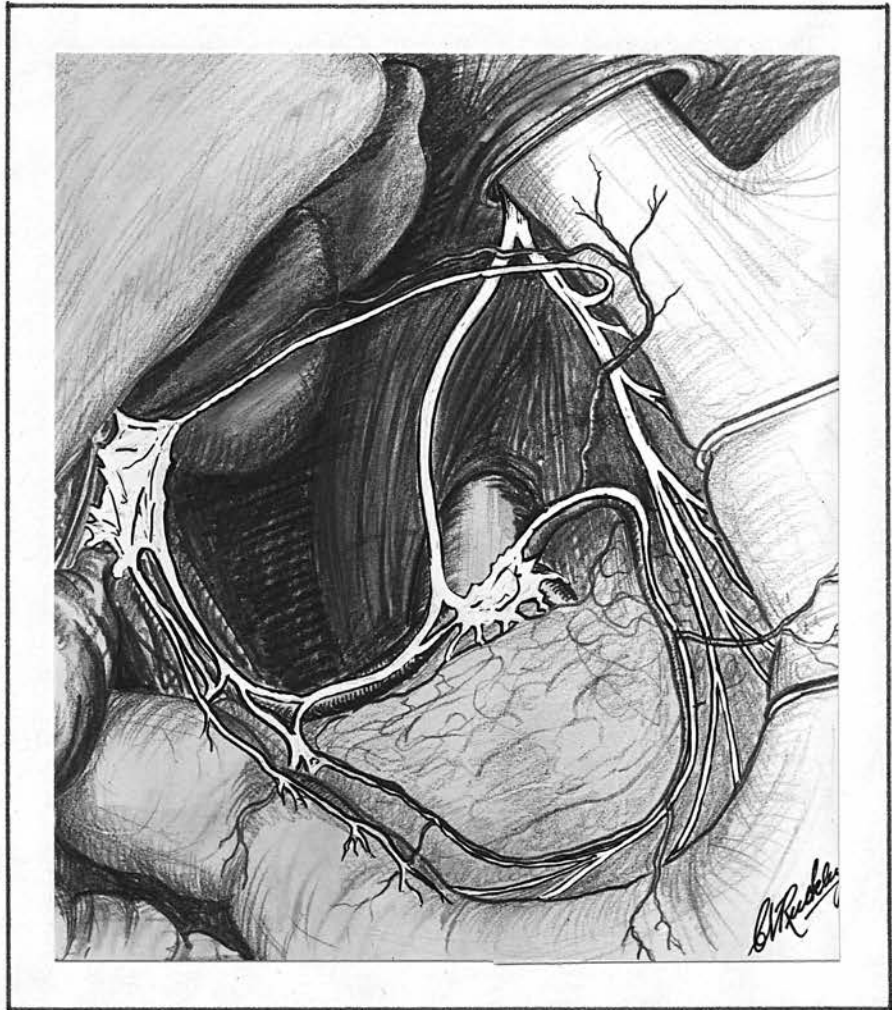


FIGURE 1, 20. Case 11.

High division of the posterior vagus. The gastric portion is shown supplying an abnormal hepatic branch.

coeliac plexus.

- 3) A combination of (1) and (2) wherein separate coeliac branches could be identified, one descending on the right crus, the other along the artery (Fig. I, 18, Case 6).

- 4) In one specimen there was no clear division.

The main posterior vagal trunk descended directly to the coeliac axis while numerous fine gastric branches sprang from it at intervals from the hiatus to the plexus. The lower gastric branches travelled some distance along the left gastric artery and its posterior divisions to reach the stomach.

- 5) The main posterior trunk descended directly towards the coeliac plexus in one specimen in the normal fashion but its gastric branches were represented by only three stout twigs which coursed close to the left gastric artery to reach the stomach.

The surgical significance of the results of this study will be discussed following the next section which deals with the anatomical findings at operation.

CHAPTER 3OPERATIVE ANATOMICAL STUDY

The preliminary anatomical studies having been completed and the operation of selective vagotomy having become established as an acceptable routine operation in the Gastro-Intestinal Unit in 1962 it was decided to study the anatomy as seen at operation. There is, after all, a difference between the leisurely pursuit with lens or dissecting microscope of vagal fibres at the dissecting table in the pinned out and perfectly illuminated specimen on the one hand, and the operative exploration of a relatively inaccessible area with limited time and visibility on the other.

Failure to recognise variations when they occur or alternatively failure to design the operation in such a way as to allow for aberrations must result either in destruction of non-gastric parasympathetic supply, incomplete vagotomy or both. Whether our anatomical studies actually resulted in more successful gastric vagotomy is discussed in Part IV.

Surgeons or their assistants were asked to record their observations as fully as possible. In many cases the operation notes were accompanied by diagrams. Latterly a proforma (Appendix I) was used to provide more standardised information.

This account is not intended to be a precise quantitative analysis but rather as a review of the spectrum of anatomy one may/

may expect to encounter when performing selective vagotomy as a routine procedure.

ANATOMICAL FINDINGS

Of the first 145 selective vagotomies 123 (85%) are judged to provide adequate anatomical descriptions.

ANTERIOR VAGUS:

Details are available for 123 patients. The main trunk was single in 77 (63%). In 46 (37%) there were two or more, but in all except 13 (10%) the anterior trunks were seen to unite at about the level of the cardia (Fig. I, 21, (1)). In 7 (6%) cases gastric branches were observed to arise high on the abdominal oesophagus or even in the thorax (Fig. I, 21, (4)). Extra fibres were also found on the oesophagus, generally on the anterior wall in a further 66 cases (55%). These were variously described as "additional fibres" or "communicating fibres" according to the surgeon's interpretation of their course.

Hepatic Division -

This division was generally easy to see and define. Always a collection of fibres rather than a single strand. They were described as a single bundle in 40 (32%), slightly separated in 51 (42%) and widely separated (2 or more bundles separated by a distance of up to 3 cm.) in 33 (26%).

Where main anterior trunks were multiple and separate earlier observations that each could give rise to hepatic branches (Burge 1961, Ruckley 1964) were confirmed (Fig. I, 21, (2)).

In/

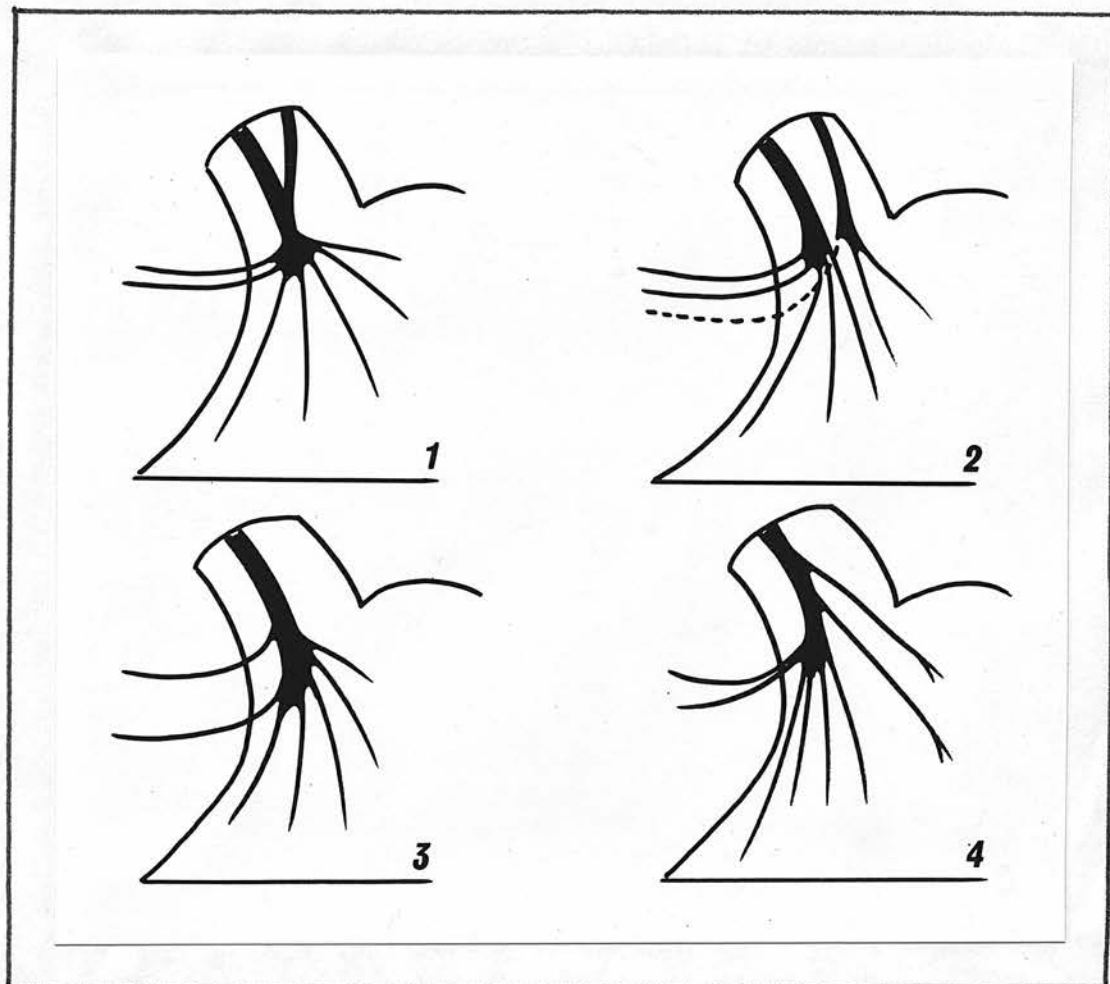


FIGURE 1, 21.

Diagram of the commoner variations of the abdominal

- vagi. (1) Double anterior trunks uniting at the cardia.
 (2) Separate anterior trunks, each supplying hepatic branches.
 (3) Widely spaced hepatic branches.
 (4) High gastric branches.



In one patient a hepatic branch was seen to arise from the posterior trunk. In 5 (3%) instances a very large accessory hepatic artery was seen to arise from the left gastric artery and, with corresponding veins, accompany the hepatic division.

POSTERIOR VAGUS:

Details were available in 117 patients.

Main Trunk -

This was described as single in 111 (95%). In 6 (5%) it was reported as double.

Coeliac Division -

This division, really a continuation of the main bulk of the posterior trunk, was exposed in 58 (50%) instances and palpated without being seen in 58 (50%). It has already been mentioned that exposure of the coeliac nerve is not now regarded as essential in this operation. In 3 (2.6%) patients the coeliac was described as double.

SUMMARY OF ANATOMICAL FINDINGS

Amalgamation of the data of the two studies results in the following conclusions:-

- 1) There are more than two main vagal trunks in more than one third of cases. This multiplicity applies almost exclusively to the anterior vagus.
- 2) In addition to the large principal trunks smaller vagal fibres can be found on the lower oesophagus in at least 55% of cases. They are more commonly to be found on the anterior oesophageal wall.

3)/

3) The hepatic division of the anterior vagus consists of many fibres. These may run in a closely-knit bundle or may be separated by as much as 3 cm. between individual strands. Exceptionally hepatic fibres may be observed to arise from the posterior vagus.

The hepatic branches may be accompanied by abnormal left hepatic vessels communicating with the left gastric pedicle.

4) The main bulk of the posterior vagus continues as the coeliac division. This substantial nerve has a variable relationship to the left gastric artery and rarely may divide into two portions which reach the coeliac ganglion by separate routes.

5) If the surgeon wishes to achieve complete gastric vagotomy and to avoid unnecessary division of non-gastric fibres it behoves him to study the vagal anatomy carefully.

The variations described do not preclude the application of a standardised technique to the operation of selective vagotomy. Their study will be rewarded by a higher incidence of satisfactory gastric vagotomy whether by the truncal or selective technique.

CHAPTER 4THE TECHNIQUE OF SELECTIVE VAGOTOMY

Critics of vagotomy as a surgical treatment of peptic ulcer generally follow one of two paths. Either they point to the high incidence of incomplete vagotomy, averaging 30% in the literature (Kay 1968) or to the high incidence of complications of which diarrhoea is the most important. The latter was the main stimulus to the development of selective vagotomy.

If the operative technique of vagotomy, whether truncal or selective, is based upon a full understanding of the anatomy, it should be possible on the one hand drastically to reduce the incidence of incomplete vagotomy and, on the other hand to achieve a selective vagotomy which preserves the maximum number of non-gastric fibres.

There are a number of ways by which selective gastric vagal denervation may be achieved. Griffiths (1962), Burge (1961) and Tanner (1966) have described different techniques. Our method owes something to each of these authors.

In particular the technique may be modified according to whether resection or drainage accompanies the vagotomy. Where drainage is planned the vagotomy should undoubtedly be done first to avoid traction on a suture-line and to minimise subphrenic contamination./

contamination. Where resection is preferred the latter consideration is outweighed by the very great advantage conferred by a mobilised, divided stomach. The gastrectomy is therefore pursued to the point where the proximal portion of the divided stomach can be retracted to the left on a clamp by the assistant, thereby making selective vagotomy very much easier (Griffiths 1962). The gastro-duodenal or gastro-jejunal anastomosis completes the operation.

The technique of selective vagotomy which is described below is based upon the foregoing anatomical studies and has been evolved during the performance of this operation on the first 145 patients at the Western General Hospital.

It was perhaps natural that an operation based upon a preliminary anatomical dissection should have tended to follow at first a similar course of careful display of vagal trunks and their branches. The technique has since evolved away from this towards the isolation and division of a series of neurovascular pedicles.

It must be emphasised that reliable selective vagotomy cannot be achieved without complete division of all branches of the left gastric artery to the stomach and terminal oesophagus. This clearance should be done in two planes corresponding to the anterior and posterior divisions of the left gastric artery. It was our practice early in the series to begin dissection low on the/

the lesser curvature serially dividing the many branches of the left gastric artery with their concurrent nerves. This method is effective but may be time-consuming and, when the vessels are obscured by fat, is apt to give rise to bleeding.

ANTERIOR SELECTIVE VAGOTOMY

We now prefer, having first taped the hepatic branches and the anterior trunk(s), to confine the dissection to a smaller area by beginning a centimetre or two below the hepatic branches and dissecting across the anterior surface of proximal stomach in an almost transverse line to the oesophago-gastric angle (Fig. I, 22).

It is unusual to meet any large vessels during this stage of the operation. By elevation of the anterior trunk the plane of dissection is generally clear. Occasionally the plane is not clear due to obesity or to inflammatory reaction. Secondary gastric ulcer is probably commoner than most surgeons realise and in this series enlarged glands on the lesser curvature were relatively common. When biopsied these glands showed reactive hyperplasia. Care must be taken in such cases to avoid damage to the muscle layers at the cardia.

POSTERIOR SELECTIVE VAGOTOMY

Whereas anterior selective vagotomy is achieved by dissection in an almost transverse plane, posterior selective vagotomy is achieved/

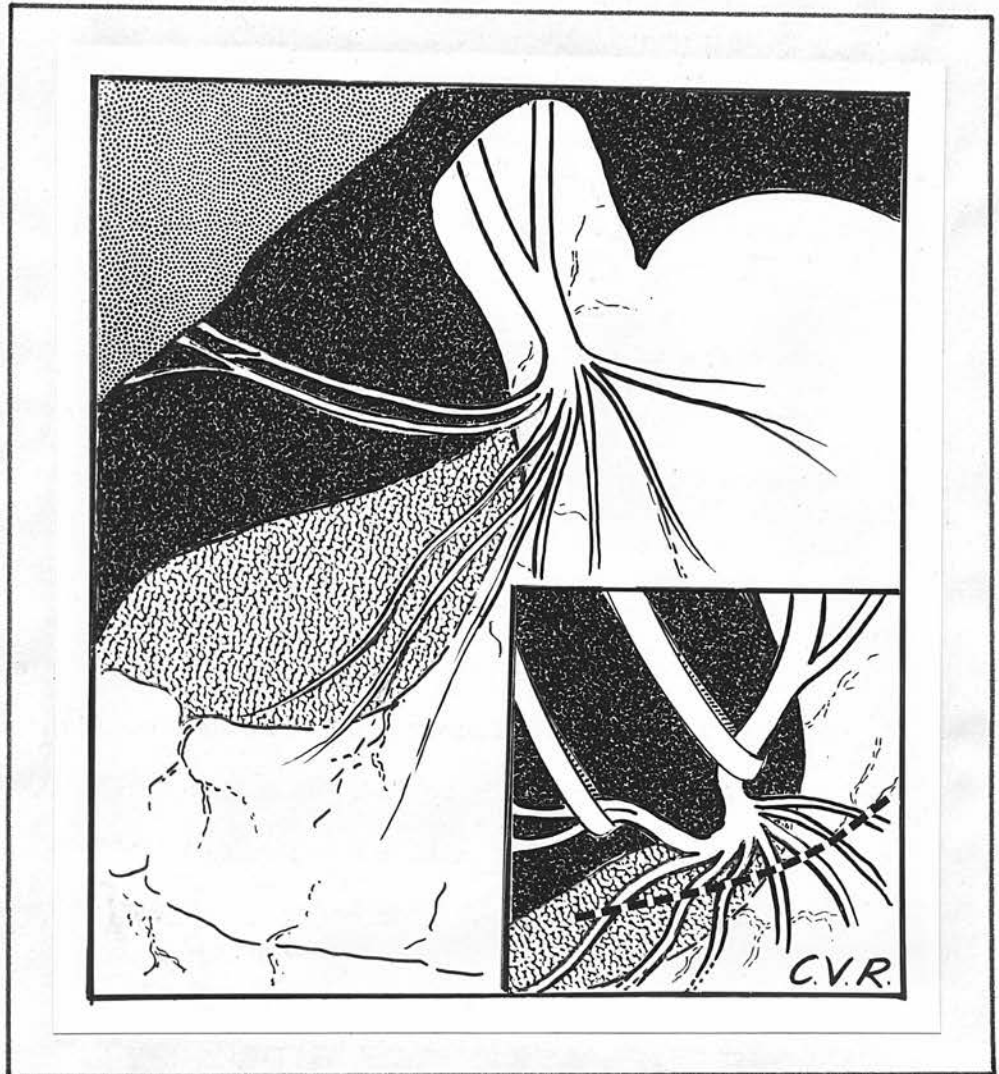


Fig I, 22. Anterior selective vagotomy. The main trunk(s) and the hepatic branches are isolated with stays of tape or polythene tube. The direction of dissection is shown by the interrupted line.

achieved in a longitudinal plane (Fig. I, 23). In so far as the posterior nerve lies at a deeper plane and is accompanied by the main portion of the left gastric artery, this part may be slightly more difficult.

It can be made much easier however by narrowing the tissue to be divided down to a neurovascular pedicle. At this point traction upon lower oesophagus and stomach to the left is necessary. This can be achieved by passing a broad tape or Paul's tube from the lesser curvature below the arch of the left gastric artery, across the lesser sac posterior to the stomach to emerge at the oesophago-gastric angle (Tanner 1966) (Fig. I, 23). The stomach is drawn to the left. The posterior vagus is taped and drawn to the right. The tissue to be divided now stands in relief. If a finger is passed from below the arch of the left gastric artery upwards between the taped posterior trunk and the right border of the oesophagus the gastric branches which require division all lie anterior to the finger. The protected coeliac division is palpable but not necessarily visible to the right (Fig. I, 23 (inset)). Tension applied to the posterior trunk allows the coeliac branch to be palpated as it curves posteriorly and to the right to the coeliac axis. Further dissection is unnecessary. The left gastric pedicle is serially divided and ligated in several portions close to the stomach and lower oesophagus.

Finally/

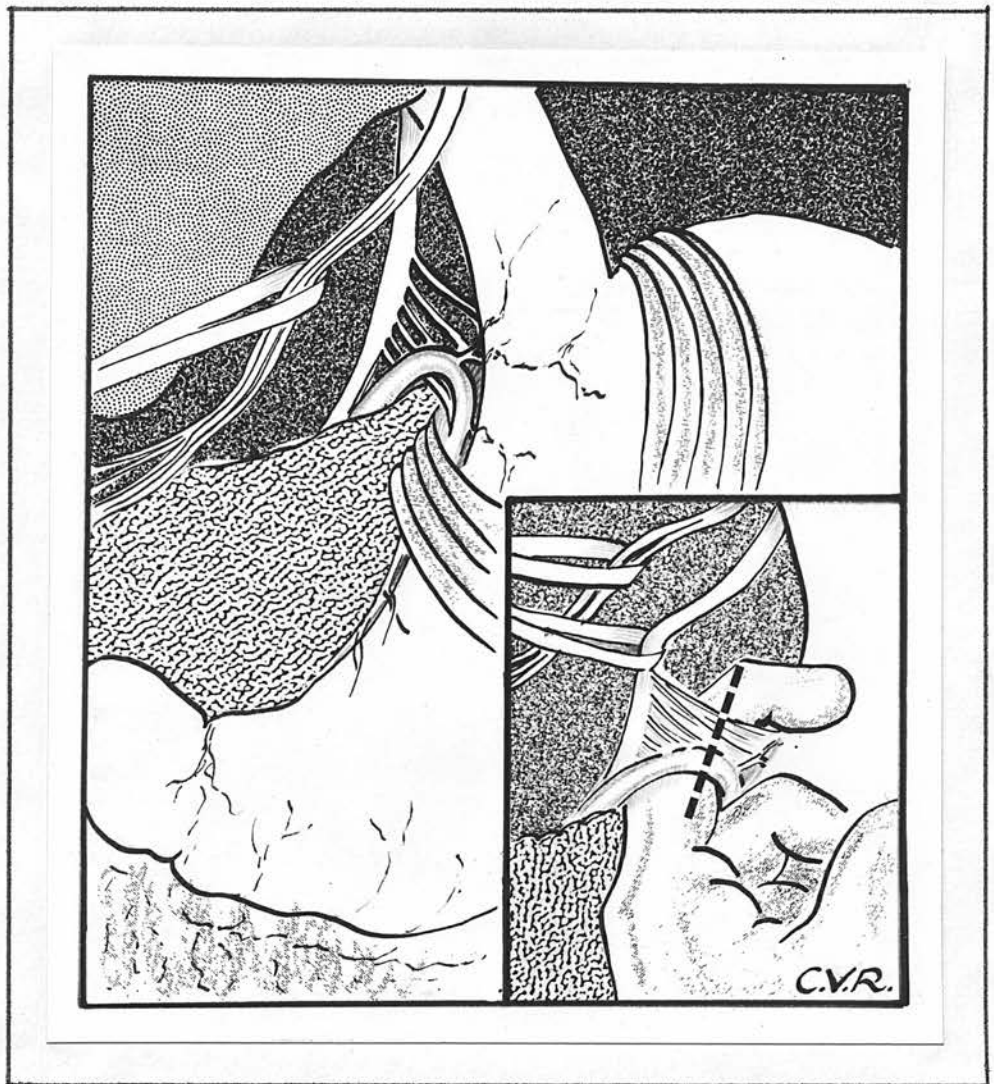


FIGURE I, 23.

Posterior selective vagotomy. The plane of dissection is displayed by the finger passed between posterior trunk and oesophagus from below the arch of the left gastric artery.

Finally, and most important of all, the lower oesophagus must be explored with the utmost care, just as in truncal vagotomy. Smaller fibres or accessory trunks passing directly down from the oesophageal plexus are sought and divided. This was not always done early in the series and its omission was certainly responsible for a number of incomplete gastric vagotomies. Extra fibres should be found in the majority of cases and it may be of interest to obtain histological confirmation when one is in doubt whether these finer filaments are nervous.

Generally no attempt has been made to divide the pyloric branch of the hepatic division, at the upper border of the antrum, for no evidence has been produced that this branch has any secretory role.

PART II

PHYSIOLOGY

THE NEURO-HORMONAL MECHANISM

o f

GASTRIC SECRETION

CHAPTER 5INTRODUCTORY REVIEW

The influence of the Pavlov school on research and thought in gastric physiology is truly remarkable. Ingenious experiments led Pavlov and his associates not only to discover the role of the vagus nerves in the activation of the acid-producing glands, but also to demonstrate that the antral duodenal area was able to exert both excitatory and inhibitory influences upon acid secretion. The mechanisms were believed to be neurogenic.

An alternative mechanism was suggested in 1906 by Edkins when he put forward his gastrin theory as an analogy to the role of secretin in the activation of pancreatic secretion. Little credence was given to this theory until 1942 when Gregory and Ivy demonstrated that perfusion of a total stomach pouch with liver extract could evoke acid secretion from a subcutaneously transplanted pouch. Even more decisive support came with the observations of Dragstedt and his associates (1950 and 1952) when they demonstrated the dramatic influence of autotransplanted antrum upon the acid secretion from total stomach pouches, Pavlov pouches and Heidenhain pouches. For example transplantation of antral mucosa into the colon resulted in profuse hypersecretion from a Heidenhain pouch. Proof that the mediator was gastrin rather than histamine awaited the isolation and synthesis of the polypeptide/

polypeptide by Gregory and Tracy in 1961.

Gastrin was known to be released by either mechanical or chemical stimuli. Distension of the stomach or massage of the antral region by extraneous forces or provoked peristalsis could be demonstrated to evoke Heidenhain pouch secretion. Similarly meat extract, peptone broth or other preparations of proteins, when perfused into the antral region, effected gastrin release. Alcohol too has proved potent in this respect.

At this stage Pavlov's concept of separate and distinct cephalic and gastric phases of secretion still remained inviolate. Conveniently the gastrin mechanism could be incorporated with the latter phase. For surgeons, following on the heels of the physiologists, this concept made rationalisation of peptic ulcer surgery easy. Assuming that in treating a patient with peptic ulcer one's aim was to reduce gastric acidity (and this of course as a sole aim is open to question) it could be argued that by doing vagotomy (or partial gastrectomy) one was amputating a distinct phase of secretion while leaving the alternative phase intact - a simple concept appealing to surgeons!

Opposition to this rigid functional separation of the two secretory phases was provided as early as 1942 when Uvnas suggested that vagal impulses were able to release gastrin from the antrum. In acute experiments with cats, he demonstrated that cocainisation or resection of antral mucosa abolished or markedly reduced the response/

response of parietal cells to vagal stimulation.

Failure by other workers to provoke secretion from a Heidenhain pouch (Janowitz and Hollander 1951) or to depress insulin-stimulated secretion from total stomach pouches by antrectomy (Oberhelman, Woodward, Zubiran and Dragstedt 1952) delayed acceptance of Uvnas's evidence.

More sophisticated experimental design however has now firmly substantiated the inter-relationship between neural and hormonal pathways. Important contributions were those of Thein and Schofield, (1959) who showed a dramatic secretory response of a totally denervated pouch to sham feeding, Gregory and Tracy (1960) who observed the same effect with tease-feeding and Nyhus, Chapman, De Vito and Harkins (1960) who abolished the insulin-stimulated response of a Heidenhain pouch by cocainisation, denervation or antroneurolysis of the antral mucosa.

The neural release of gastrin then is proved. Of considerable importance to the surgeon are the further steps that have been taken, notably by elegant experiments at the Karolinska Institute (Olbe 1964; Uvnas, Emas, Fyro, and Sjodin 1966). These workers showed that the sham feeding response of Pavlov pouch dogs was almost abolished by antrectomy. They further showed that the response could be restored by subthreshold doses of exogenous gastrin.

Conversely/

Conversely the Pavlov pouch secretory response to sham feeding could be augmented by simultaneous mechanical stimulation of the antrum. Their conclusion was that "under physiological conditions an interplay between gastrin and vagal impulses is essential for the normal course of the secretory response to a meal. Each of the two stimuli may under experimental conditions break through the stimulatory threshold of the HCl secretion glands. It is doubtful, however, if they ever do this under physiological conditions". (Uvnas, Emas, Fyro and Sjodin 1966).

Figure II, 1, illustrates diagrammatically and in very simple form the factors acting to promote acid release. Precise anatomical relationships such as the site of production and action of histamine and the relationship of post-ganglionic parasympathetic nerve endings to the secretory cell have not yet been determined. It is possible, for example, that the various mechanisms which promote acid-pepsin secretion do so by influencing gastric submucosal blood flow. Whether the observed association of increased submucosal blood flow with increased secretion is a causal one or merely a secondary effect reflecting the increased metabolic activity in the tissues is not known (Jacobson 1965). The balance of evidence appears to suggest that gastric secretion and submucosal vasomotor changes can occur independently (Bell 1968).

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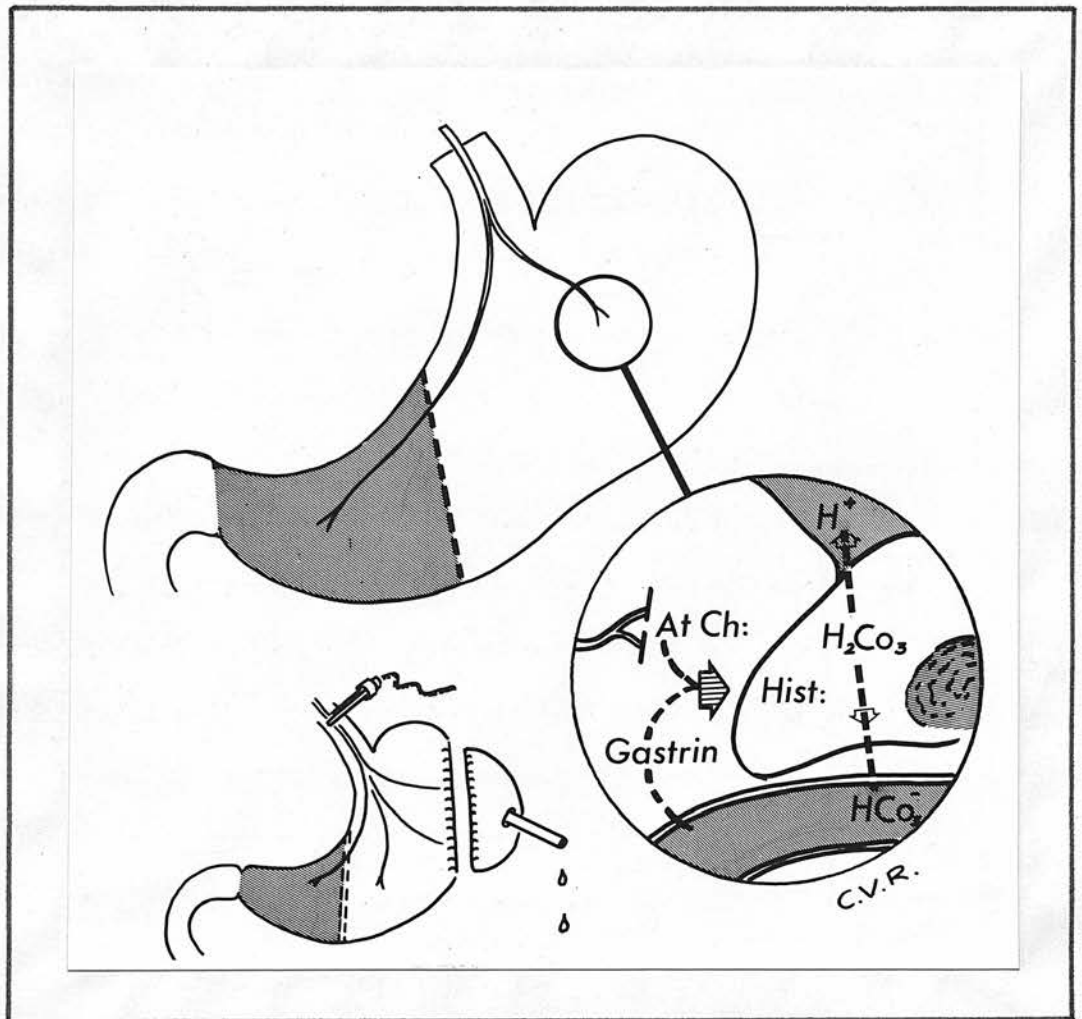


FIGURE II, 1.

A simplified diagram of the principal known factors in acid-pepsin stimulation. The vagus acts both directly upon the secretory cells and indirectly via the antrum (shaded). The denervated Heidenhain pouch (left lower diagram) can be used to demonstrate the neuro-hormonal path provided that acid-inhibition of the antrum is avoided. Vagally-released acetyl-choline and blood-borne gastrin are depicted as acting synergistically from outside the cell. Histamine may be released within the cell.

In summary, animal experiments appear to show that nervous and humoral mechanisms cannot operate effectively independent of each other.=

In this area of gastric physiology two principal questions will be discussed further:-

1. Is there any evidence of similar synergism between the neural and humoral pathways in human gastric function?
2. If such a synergistic relationship exists, what is its relevance to the design and assessment of peptic ulcer surgery?

To answer the first question evidence obtained in clinical follow-up and secretion studies at the Gastro-Intestinal Unit, Western General Hospital is analysed together with a review of data available in the literature.

Question 2 will be discussed in the light of canine gastric secretion studies carried out by the author.

CHAPTER 6EVIDENCE FOR THE INTER-RELATIONSHIP OF THE NEURAL AND
HUMORAL PATHWAYS OF GASTRIC SECRETION IN HUMANSThe Effects of Partial Gastrectomy upon Acid Output

In 1964, as part of the studies on vagal function described here, a review of post-operative secretion tests was begun. It has been part of the policy of the Gastro-Intestinal and General Surgical Units, Western General Hospital, Edinburgh, to carry out post-operative maximal and insulin secretion tests wherever possible. All categories of peptic ulcer patients have undergone post-operative histamine or latterly pentagastrin (Peptavlon) 'maximal' acid tests, while those treated by vagotomy have in addition undergone tests of insulin-stimulated secretion to assess the completeness of vagotomy. The technique and interpretation of the insulin secretion test will be dealt with more fully later. The results of a number of those tests are to be used as evidence in the present context. It was soon apparent, upon undertaking the above review, that some results could only be explained on terms of a functional inter-relationship between vagus and antrum. These data are presented in Table II, 1, and incorporate results of 180 insulin secretion tests. Hollander's data have been interpreted by his own criteria while the Western General Hospital series (W.G.H.) has been interpreted by multiple criteria. For the purposes of the present argument, the absolute values upon which/

INSULIN SECRETION TESTS AFTER VAGOTOMY:
COMPARISON OF DRAINAGE AND RESECTION

Type of Operation	No. of Cases	Per cent Positive
<u>Vagotomy & Drainage</u>		
Hollander 1950	26	43%
W.G.H. 1969	65	37%
	Mean	40%
<u>Vagotomy & Resection</u>		
Hollander 1950	58	12%
W.G.H. 1969	31	14%
	Mean	13%

TABLE II, 1

which the criteria are based are not relevant for it is the relative differences in results between operation groups to which particular attention is drawn. It will be seen that the incidence of positive tests after vagotomy and drainage is 40%. After vagotomy and partial gastrectomy the incidence is 13%. Since there is no reason to suppose that surgeons carry out better vagotomies when combined with gastric resection we are left with the conclusion that the latter procedure influences the outcome of the former, or, more specifically, that removal of the distal stomach reduces the ability of the parietal cells to respond to vagal stimulation. Evidence will be provided later to show that pepsin-release behaves differently.

What then is the effect of antrectomy alone on vagally-stimulated acid secretion? Little evidence is available on this aspect. Since the insulin test is a test of completeness of vagotomy, there has been no clinical indication to apply it after partial gastrectomy alone.

Neither is adequate information available in the literature on the effect of gastric resection upon vagally stimulated secretion in humans. The secretory response to a meat meal was shown to be reduced by partial gastrectomy in dogs by McCann (1929) and Lewis (1938). Glass and Wolff in 1950 demonstrated that/

that the acid-stimulating effect of insulin was diminished and often abolished following resection of the distal end of the stomach while the pepsin and muco-protein responses were undiminished. Similar results to sham feeding in peptic ulcer patients after partial gastrectomy were noted by Noring (1951). Waddell (1957) showed that there was no significant difference in insulin-stimulated secretory response between a group of patients who had had partial gastrectomy with vagotomy and a group who had had partial gastrectomy alone; both groups were markedly hypochlorhydric. These results are shown in Table II, 2. Attention is also drawn to a third group, namely a series of patients who had partial gastrectomy and who developed recurrent ulcer. It is evident that the vagally-stimulated secretion in this latter group was high. It is postulated here that this high response was made possible because the surgeon failed to excise all antral tissue at the time of the partial gastrectomy, thus allowing the neuro-hormonal synergism to persist. Evidence that this, as a cause of persisting high secretion and recurrent ulceration after partial gastrectomy, is not merely conjectural is provided from a number of sources.

Important data are provided by Waddell in a series of patients undergoing antral exclusion operations, (two-thirds to three-quarters Bilroth II partial gastrectomy with retained excluded antrum). Six patients after this procedure had an average/

THE EFFECTS OF VARIOUS OPERATIONS UPON
INSULIN-STIMULATED ACID SECRETION

Anatomic Arrangement	No. of patients	Volume ml/hr.	Average pH	m.Eq. Free Acid
Intact Stomach	75	129	1.3	10.5
Hemigastrectomy with Vagotomy	18	56	5.6	0.2
Partial Gastrectomy ($\frac{2}{3}$ - $\frac{3}{4}$)	8	41	5.0	0.6
Partial Gastrectomy with recurrent ulceration	5	135	1.8	5.7

(From Waddell, 1957)

TABLE II, 2

average of 3.3 m.Eq. of full acid per hour to insulin stimulation, whereas after partial gastrectomy with antral excision (8 patients) the mean free acid output was 0.6 m.Eq. per hour (Waddell 1956).

Other workers have clearly demonstrated the ulcerogenic potential of retained antral tissue in experimental animals (Harrison, Williams, Pisesky, Husain, Silbermann, Francis and Irvine 1961).

CHAPTER 7THE RELEVANCE OF THE NEURO-HORMONAL CONCEPT TO THE
DESIGN OF PEPTIC ULCER SURGERY

The evolution of our knowledge of the functional importance of the antral gastrin mechanism has been outlined. Clinical evidence has been provided for the relevance of this mechanism to the management of peptic ulcer both in the design of surgery and the interpretation of its results.

Upon reviewing these data at a clinical level it seemed necessary to examine the vagus-antrum relationship more closely in the experimental laboratory. The following section describes the results of studies undertaken in the Halsted Research Laboratory, University of Colorado Medical Center, Denver, Colorado, while the author was the recipient of a Research Fellowship under Dr. William R. Waddell for one year beginning in October 1966.

The term 'gastric antrum' requires preliminary definition.

The Antrum

Although earlier workers had noticed differences between the cell types in the glands of the fundus, body and prepyloric areas of the stomach, the first clear description of the gastric cell types is attributed to Bensley (1899). He showed that the pyloric glands were composed of cells similar to the mucous neck chief cells of the fundic glands. These glands do not secrete acid but produce an alkaline, viscous juice.

Among/

Among the humoral substances claimed to originate in the prepyloric or antral region are an inhibitory hormone or chalone (Harrison, Lakey and Hyde 1956, Jordan and Sand 1957) pepsin (Grossman and Marks 1960) and gastrin (Edkins 1906).

Unfortunately the sharp delineation between the mucosa of the antrum and corpus so easily seen macroscopically in the stomach of the rat, is not present in the canine or human stomach.

Although the trained observer can detect a mucosal change macroscopically at operation the transition zone is ill defined and requires histological confirmation.

The most authoritative study of the morphology of the antrum has been made by Oi, Oshida and Sugimura (1959). From data derived from 207 resected human stomachs with gastric ulcer they showed the average width of the transition zone to be 3.8 mm. on the lesser curvature and 3.0 mm. on the greater curvature. They showed also that this zone might be as much as 16 cm. up the lesser curvature from the pylorus.

Thus, it is concluded by Ruding and Hurdes (1953), who carried out a similar study, that removal of the antrum might require excision of as much as 80% of the lesser curvature with corresponding parts of anterior and posterior walls and greater curvature. It is often taught that a tongue of antrum extends up the lesser curvature and resections such as the Schoemaker-type are/

are used to allow for this. It is evident from the work of a number of authors including those cited above that this is not correct. The upper border of the antrum may extend further proximally on the anterior or posterior surfaces or the greater curvature and the proximal line of antral resection should therefore be carried across the stomach to remove an equal length of greater curvature.

It must be acknowledged that the extent of the antrum as judged by the extent of the alkaline-secreting mucosa may vary according to the duodenal or gastric disease present.

For example in patients with gastric ulcer the pH-electrode mapping technique shows the transition zone to be higher up the stomach than in normal or duodenal ulcer subjects (Capper, Laidlaw, Richards and Buckler 1963) presumably as the result of replacement of acid-pepsin-secreting mucosa by that of the pyloric type.

It follows that if the surgeon wishes to resect the antrum or alkaline area in its entirety a mapping device is required.

Antral Mapping Techniques

Apart from the pH-electrode method of Capper already mentioned, a number of techniques have been described. They are based either upon the application of a pH-indicator substance such as prussian blue, congo red, bromophenol blue or litmus to the histamine-stimulated mucosa or upon the selective excretion of/

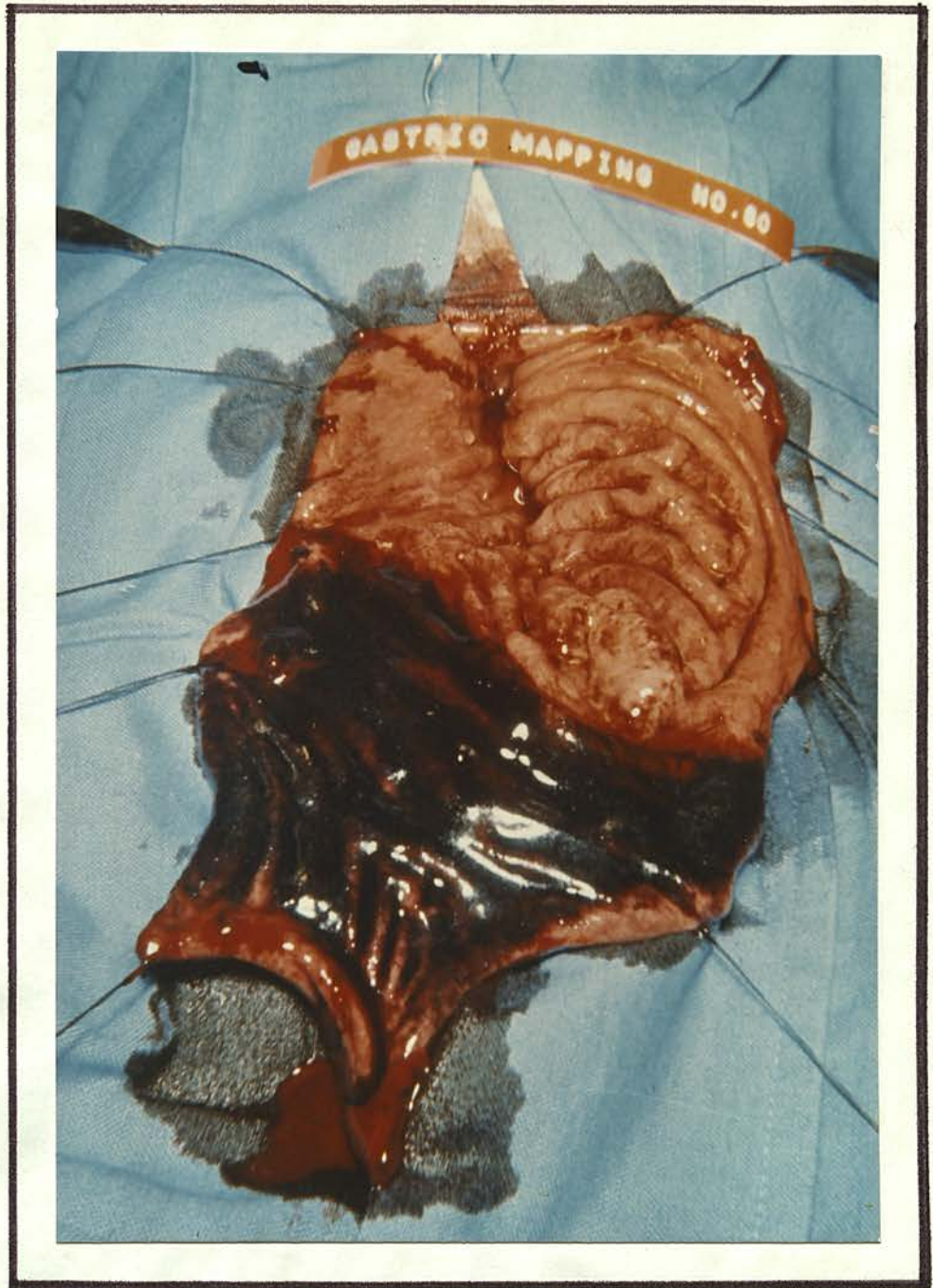


FIGURE II, 3.

Mapping of the canine stomach at operation.
Litmus powder on the antral mucosa remains blue while
that on the corpus becomes red.



FIGURE II, 4.

Close-up of junction between antrum and corpus.

of an intravenously administered dye such as toluidine blue or neutral red by the secreting mucosa of the corpus. These methods have been reviewed by Moe, Klopfer and Nyhus (1965). The method employed in this study was that of Bergström and Broomé (1964). After opening the stomach by a longitudinal incision finely powdered litmus is insufflated over the mucosal surface. Histamine acid phosphate, 0.04 mg./kg. given subcutaneously 10 - 15 minutes prior to the incision produces a copious acid secretion. The resulting demarcation is shown in Figures II, 3 and 4. Gastric mapping techniques have been used in humans during peptic ulcer surgery (Bergström and Broomé 1964; Osborne and Frederick 1965; Moß, Klopfer and Nyhus 1965; Capper, Butler, Buckler and Hallett, 1966).

Although there is now evidence which localises the cellular origin of gastrin (McGuigan 1968) it remains to be seen whether antral mapping by the methods described is appropriate in terms of the gastrin-producing area.

CHAPTER 8THE EFFECT OF COMPLETE AND INCOMPLETE ANTRECTOMYUPON VAGALLY-STIMULATED SECRETIONS IN DOGS

The review of clinical evidence (Part II, Chapter 6) demonstrated that antrectomy reduces vagally-stimulated gastric secretion. This effect is achieved despite the fact that the production of gastrin, or gastrin-like polypeptides, is not limited to the pyloric antrum (Lai 1964; McGuigan 1967; Mutt and Jorpes 1967; Celestin, 1967).

For the surgeon the choice lies between drainage and resection as companions for vagotomy. Most authors agree that resections incur a higher mortality and morbidity rate while drainage procedures carry a greater risk of recurrent ulcer. Where resection is the choice many authors have reported success with very limited (25% or less) distal resections (Palumbo and Sharpe 1965; Schuberth and Westerholm 1965). Others have advocated delineation and resection of the entire antrum (Osborne and Frederick 1964; Bergström and Broomé 1964). The methods involved and the extent of resection which may be necessary in the latter instance have already been outlined.

Few would dispute that mortality and morbidity rise with the extent of resection. How necessary then is it to resect all/
all/

all antral tissue? In every-day practice many so-called antrectomies are undoubtedly incomplete, the more so as the surgeon is prone to overestimate the proportion of stomach removed at partial gastrectomy (Wheeler, 1966). As noted earlier, residual antral tissue has been indicted as a cause of recurrent ulcer (Harrison, Williams, Pisesky, Husain, Silberman, Francis and Irvine 1961).

It was the purpose of this study to determine what proportion of vagally-stimulated secretion could be attributed to intact antrum and what was the secretory influence of residual antral tissue by comparing the responses after total and subtotal antrectomy.

Materials and Methods

Fifteen mongrel dogs ranging in weight from 12 - 23 kgs. were each provided with a cervical oesophagostomy (Komarov and Marks, 1958) and a gastric cannula situated 3 - 6 cms. from the pylorus. This type of oesophagostomy allows occlusion of the oesophagus during a secretion test, thus removing saliva from the collection without causing the animal any apparent discomfort. The method is described and illustrated in Appendix II. Secondly, it provides a convenient route whereby materials may be instilled into the stomach or the stomach washed out through the opened cannula. Between tests the dog is able to feed normally/

normally, and provided that site and size of the stoma are carefully gauged there is no nutritional deficit. During this experiment, except for the early post-operative periods, all dogs were able to maintain or increase their weight.

Phase 1

After a convalescent period of at least three weeks followed by a number of sham tests for training purposes, each dog underwent a series of insulin stimulated gastric secretion and gastric recovery tests.

Phase 2

The secretory pattern of the whole stomach having been established in all dogs, they were randomly divided into three groups: total antrectomy (6 dogs), sub-total antrectomy (5 dogs) and controls (4 dogs).

At operation gastric mapping was carried out by the method described on page 78 and illustrated in Figures II, 3 and II, 4. This method provided good demarcation, later confirmed histologically as occurring at the transitional zone. Low-power magnifications of tissues obtained at operation or autopsy are shown in Figures II, 10 - 12.

The/

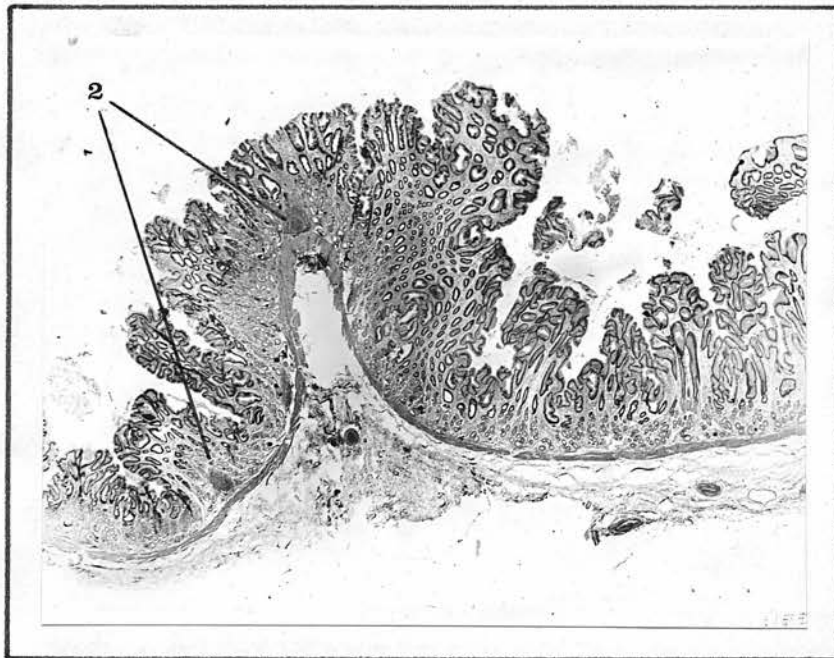


FIGURE. II. 10.

SECTION FROM RESECTED ANTRUM. Dog No: 149. Low power magnification (x 10) showing typical convoluted gastric mucosa consisting of mucus-secreting glands, coiled at their bases. Lymph follicles (2) can also be seen.



FIGURE II, 11.

COMPLETE ANTRECTOMY. Dog no 368. Section across anastomosis (arrowed) showing corpus type of mucosa anastomosed to duodenal mucosa. (Magnification x 10).

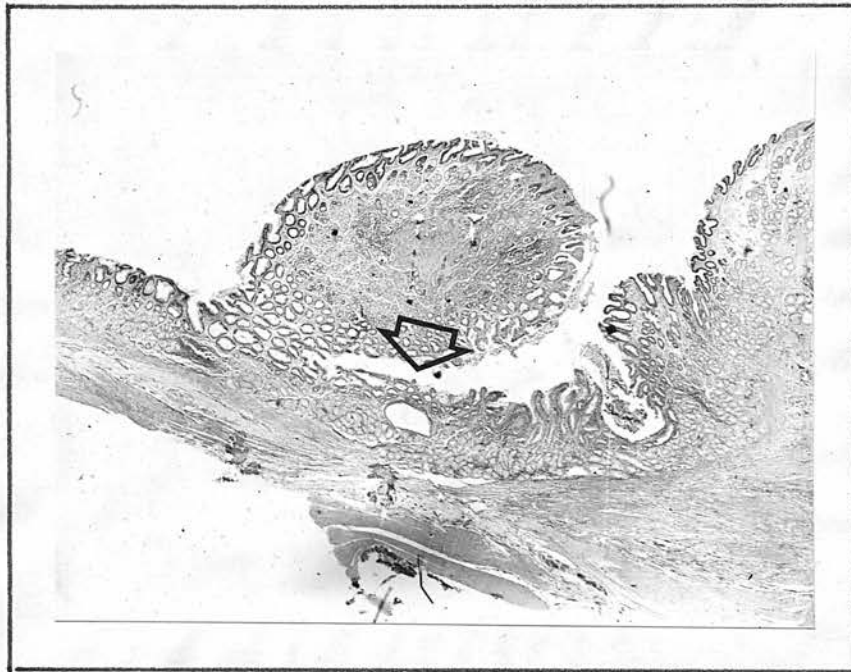


FIGURE II, 12.

SUBTOTAL ANTRECTOMY. Dog No: 219. Section across gastro-duodenal anastomosis (arrowed). Pyloric mucosa joins duodenal mucosa.

The gastric preparations are shown in Figure II, 5. In the total antrectomy group (C) the line of resection was made approximately one centimetre proximal to the mapped junction. The line of resection in the subtotal group (B) was approximately one centimetre distal to the junction. In two dogs in the latter group a cuff of antral tissue was left at the pylorus instead of at the proximal border. These two animals required pyloroplasty within two weeks because of gastric retention. In all animals in the subtotal group, an estimated 80 - 90% antrectomy was carried out.

In the resections with the two exceptions noted, the first 1 - 2 cms. of duodenum were also removed and in all the dogs a Bilroth I type of anastomosis was made. In every case it was necessary to reposition the cannula.

In the control group (Fig. II, 5, A) lesser gastric operations were carried out, namely gastrotomy with biopsies (2) and pyloroplasty with biopsies (2). After a three to four week period of convalescence secretion and recovery tests were repeated.

Insulin Secretion Tests

In both phases of the experiment a minimum of three tests was carried out upon each dog. Each test was conducted as follows:-

After/

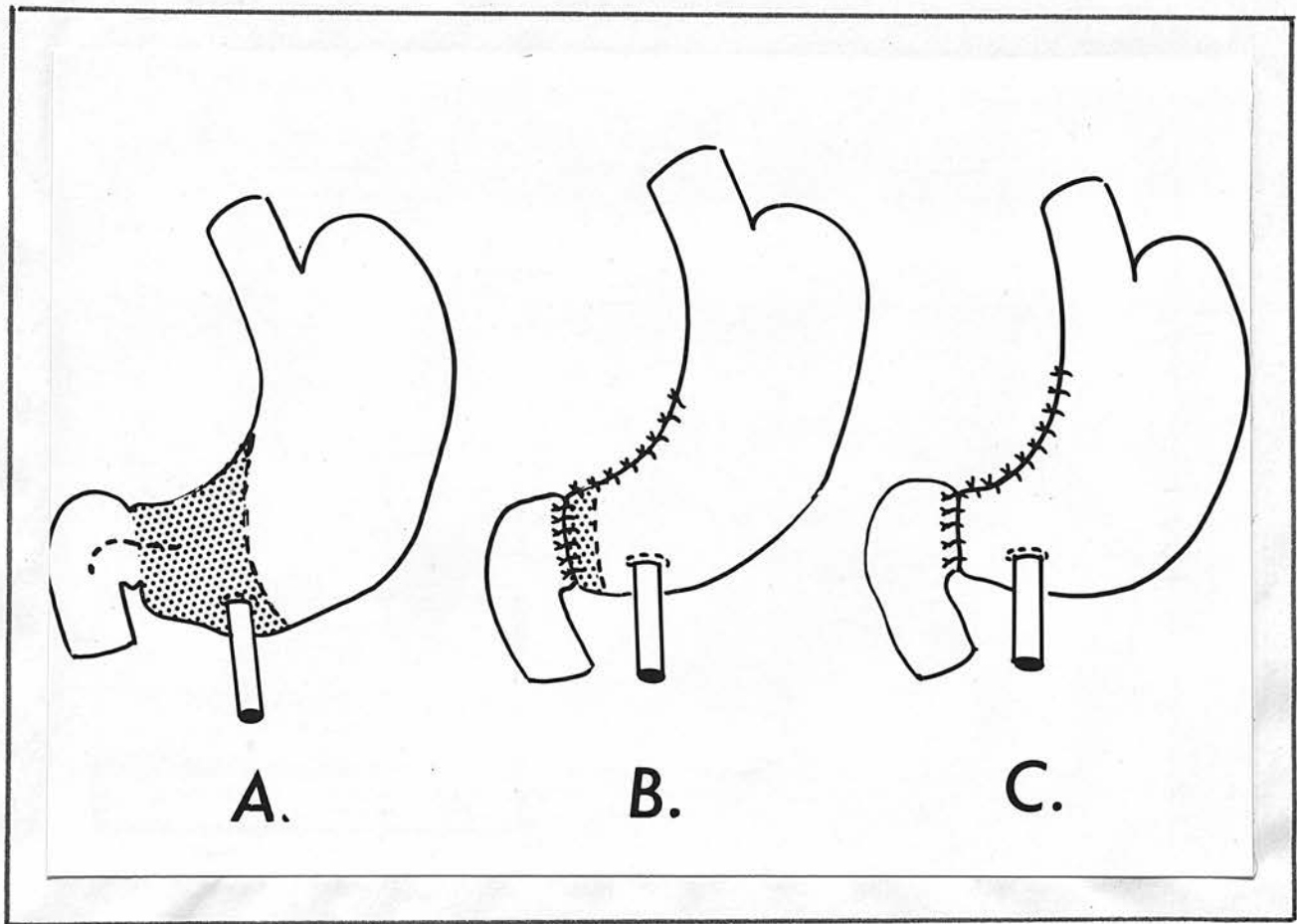


FIGURE II, 5.

Gastric preparations.

- A. Control.
- B. Sub-total antrectomy.
- C. Total antrectomy.

After a sixteen-hour fast, a half-hour basal collection was made. If the dog was found to be secreting acid during this basal period, the test was postponed until another day. An exception to this was one animal in the subtotal group which throughout the eleven months of study was found always to secrete basal acid. Insulin was given intravenously (0.15 u./kg. body weight). This dose was selected as that likely to give a high, reproducible response (Hirschowitz and O'Leary, 1964). A blood sample for glucose estimation by the glucose oxidase method was taken before, 40 and 120 minutes after the insulin injection.

The gastric juice was collected every seven and a half minutes for two and a half hours. It was pooled into 15 minute samples and titrated against 0.1 N Sodium Hydroxide to pH 7.0 using a Beckman pH meter. In ten dogs pepsin estimations were also carried out by the radio-iodinated serum albumin method of Klotz and Duvall (1957). In 128 tests gastric recoveries were also determined by the slow instillation of carbon-14 labelled polyethylene glycol (PEG) into the oesophagostomy with a fine 9 inch polythene cannula. Aliquots of the gastric juice were counted in a Packard Tri-Carb Scintillation Counter. This technique is described in detail in Appendix III.

Results/

Results

These data are derived from 150 gastric tests carried out over a period of eleven months. The majority of dogs, upon repeated testing, were consistent. A few, despite satisfactory collections, tended to be erratic in degree or pattern or both. These latter underwent extra tests in an attempt to establish more representative results.

Secretory capacity did not clearly relate to size of animal. The response to the standard dose, as also to other doses and other stimulants, varied greatly between different dogs. For example, the smallest dog in the group (12 kgs.) produced a mean two-hour output in Phase 1 of 37.7 m.Eq. while at the other extreme a dog of 22 kgs. produced only 2.3 m.Eq. despite hypoglycaemia of less than 40 mgs.%.

In all except two tests the 40 minute blood sugar was below 45 mgs.%. In the two failures it was thought that insulin escaped outside the vein through faulty injection technique. The results of these two tests were discarded. The mean blood glucose at 40 minutes in the remainder was 27.5 mgs.%.

Phase 1 - The Intact Stomach

The standard acid response to insulin 0.15 u./kg. (Fig. II, 6) was a sharp rise occurring in the second 15 minute collection.

A/

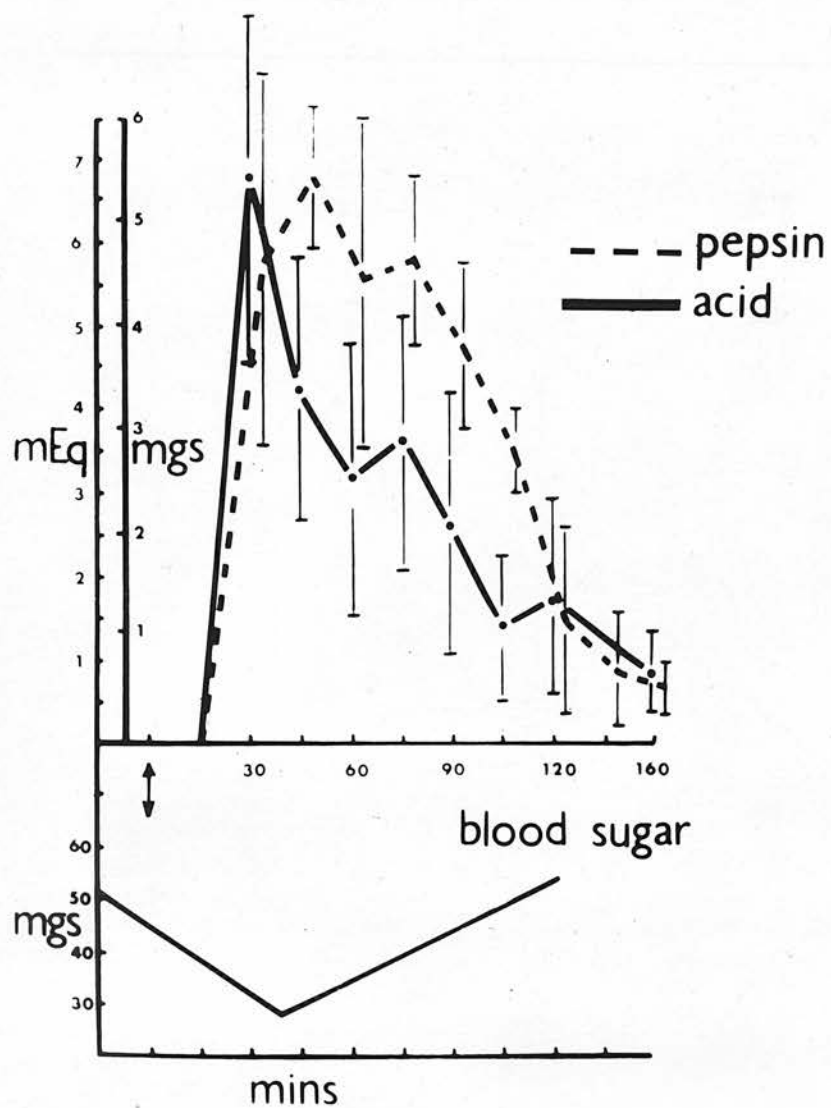


FIGURE II, 6.

The standard canine acid-pepsin response to intravenous insulin 0.15 units per kilogram. (Means with one standard deviation).

A peak was reached within the first 45 minutes. This was followed by a rapid decline to near basal levels at the end of 120 minutes. The pepsin output showed a similar pattern except that the highest concentrations were commonly found towards the end of a test. When the volumes were very low, concentrations of up to 500 mgs.% were not uncommon while at the period of peak volume, output, concentrations rarely exceeded 200 mgs.% and were usually considerably lower. In comparison with the acid output, therefore, this commonly resulted in a less pronounced peak in the first 45 minutes and a flatter curve or even a second peak in the second hour.

The mean C-14 PEG recovery from these whole stomach studies was $86.2 \pm 1.8\%$ (Standard Error) (Table II, 3).

Phase 2 - Total and Subtotal Antrectomy

With the exception of one dog (No. 1) (Fig. II, 7) in the subtotal antrectomy group and all the controls every dog showed a fall in acid secretion in this phase of the experiment, although the pattern of the response did not alter (Figs. II, 8 and II, 9). The results expressed as two-hour output are detailed in Table II, 4. Pepsin responses were less consistent and showed no appreciable fall in any group (Table II, 5).

Expressing the Phase 2 response as per cent of Phase 1 with one standard deviation from the mean, the mean reduction in acid/

CARBON - 14 LABELLED POLYETHYLENE GLYCOL RECOVERIES

Preparation	No. of Tests	Mean % Recovered	S. Error
Whole stomach	55	86.2%	$\pm 1.8\%$
Pyloroplasty	20	86.2%	$\pm 3.2\%$
Gastric resection	53	83.9%	$\pm 2.3\%$

TABLE II, 3

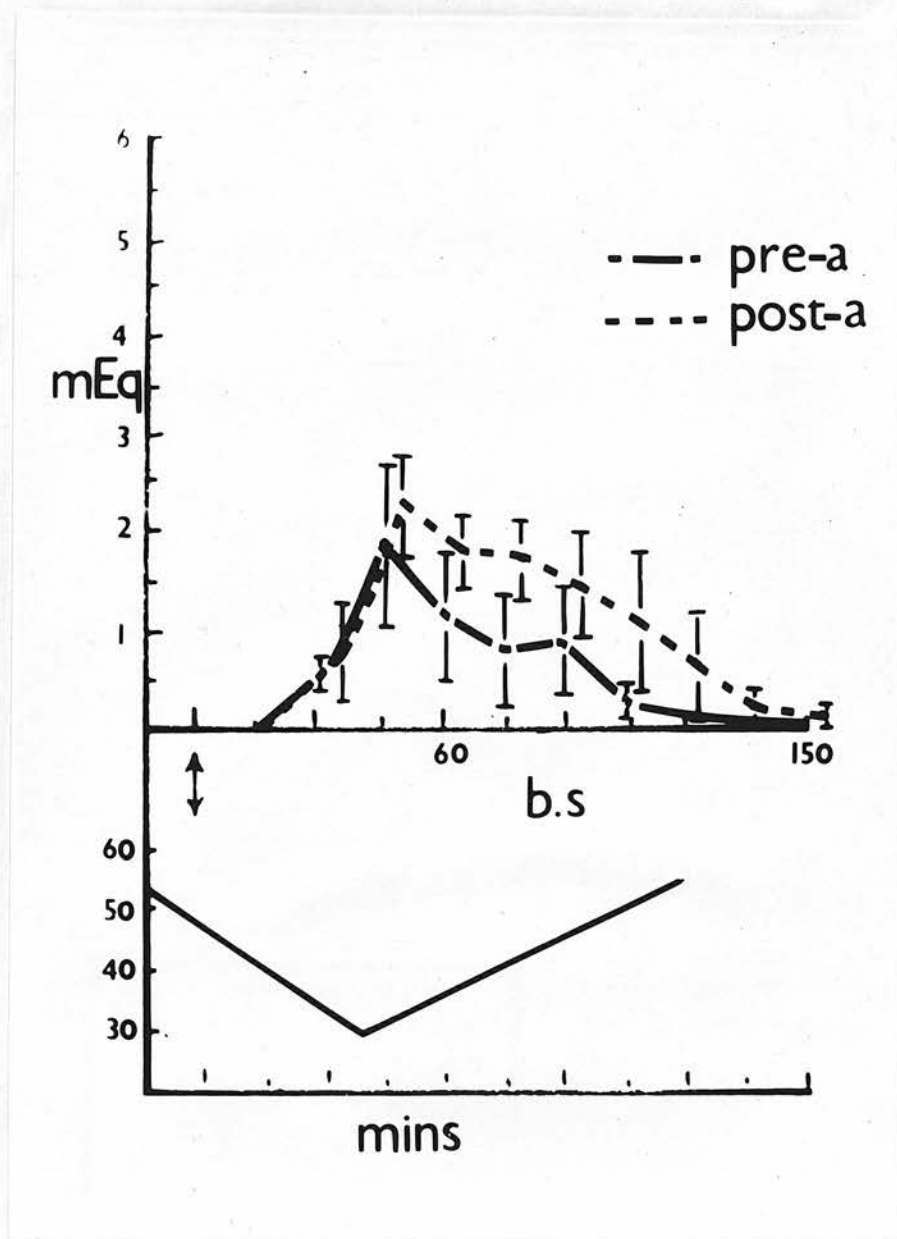


FIGURE II, 7.

Dog No: 31. Atypical response after subtotal antrectomy.
(Means \pm one standard deviation.)

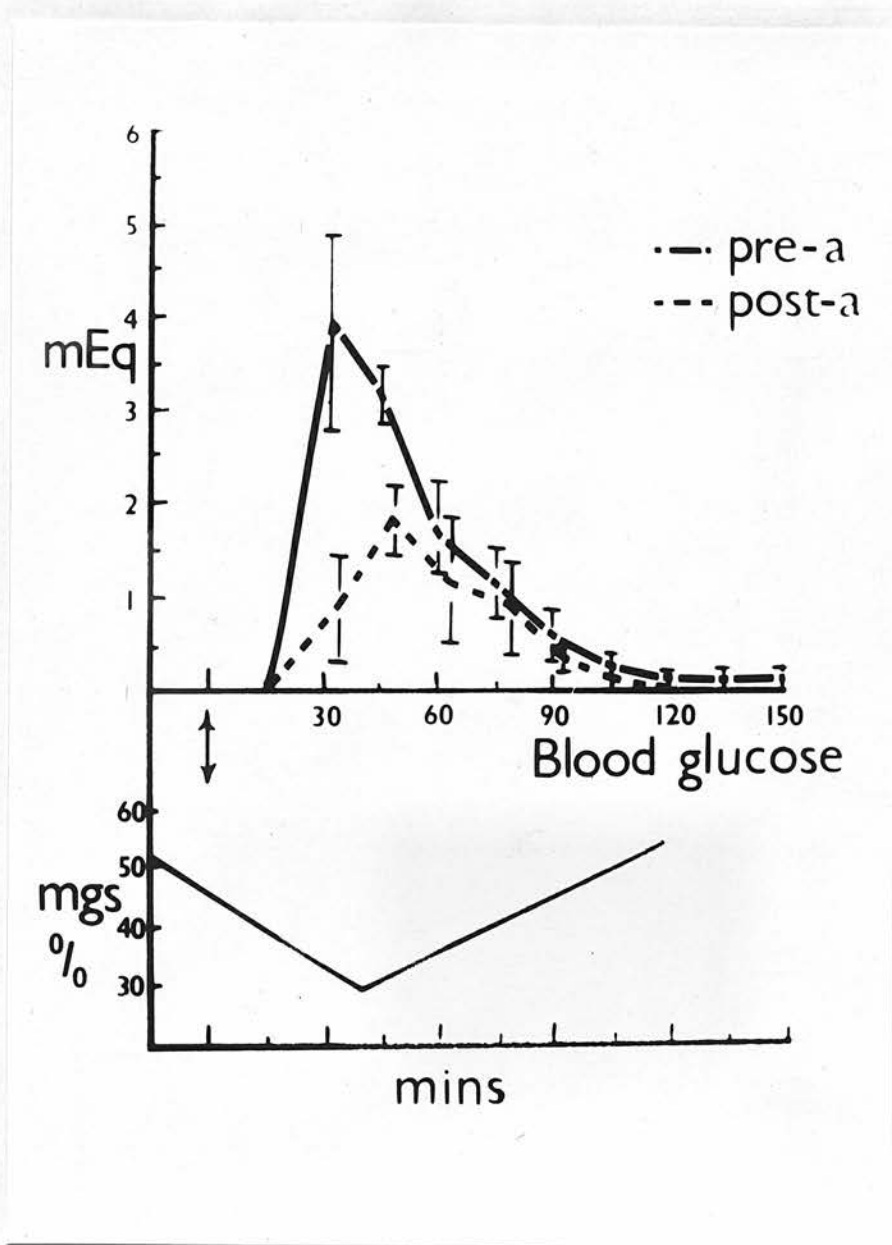


FIGURE II, 8.

Dog No; 7. The acid response before and after subtotal antrectomy. (Means \pm one standard deviation).

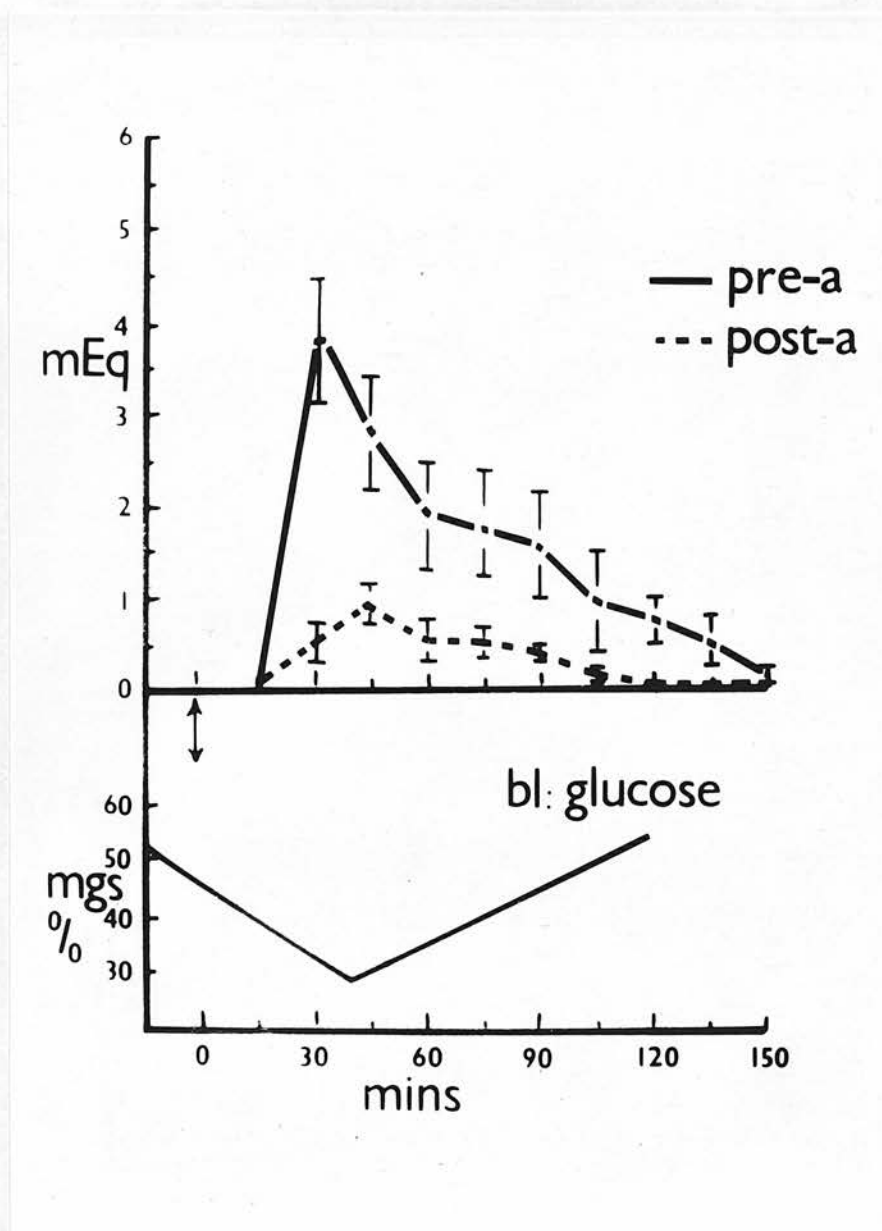


FIGURE II, 9.

Dog No: 2. The acid response to 0.15 u/kg insulin before and after complete antrectomy. The means \pm one standard deviation of three tests are shown.

ACID: THE TWO HOUR OUTPUT
(WITH STANDARD DEVIATIONS)

Dog No.	Phase 1 (mEq)	Phase 2 (mEq)	Phase 2/Phase 1 (per cent)
<u>CONTROLS</u>			
4	26.0 \pm 6.3	29.0 \pm 1.4	111.5%
5	11.5 \pm 1.8	12.4 \pm 2.5	107.8%
8	17.9 \pm 3.2	22.9 \pm 2.8	127.9%
15	7.8 \pm 2.0	6.2 \pm 1.4	79.4%
		Mean	106.7 \pm 17.5%
<u>SUB-TOTAL ANTRECTOMY</u>			
1	6.4 \pm 3.3	9.3 \pm 2.0	145.0%
14	27.4 \pm 3.0	6.0 \pm 1.2	21.8%
6	8.7 \pm 0.4	4.4 \pm 1.7	50.6%
7	14.0 \pm 3.0	4.7 \pm 3.2	31.8%
12	2.3 \pm 1.4	2.1 \pm 0.8	91.3%
		Mean	68.1 \pm 45.2%
<u>TOTAL ANTRECTOMY</u>			
2	13.4 \pm 3.8	2.9 \pm 0.1	21.6%
11	4.1 \pm 1.4	2.3 \pm 1.0	56.0%
9	22.4 \pm 4.5	9.1 \pm 4.1	40.6%
10	13.3 \pm 3.8	5.7 \pm 0.5	42.8%
13	37.7 \pm 7.3	9.9 \pm 2.5	26.3%
3	37.0 \pm 5.7	16.8 \pm 4.6	45.4%
		Mean	38.8 \pm 14.1%

TABLE II, 4

PEPSIN: THE TWO-HOUR OUTPUT
(MEANS WITH STANDARD DEVIATIONS)

Dog No.	Phase 1 (mgms)	Phase 2 (mgms)	Phase 2/Phase 1 (per cent)
<u>CONTROLS</u>			
4	72.7 \pm 14.1	85.1 \pm 10.3	117.1%
5	43.9 \pm 7.1	44.8 \pm 5.7	102.1%
8	40.6 \pm 9.1	38.2 \pm 7.1	94.1%
		Mean	104.4 \pm 9.5%
<u>SUB-TOTAL ANTRECTOMY</u>			
1	40.1 \pm 8.2	66.4 \pm 3.5	165.6%
6	51.3 \pm 8.1	49.7 \pm 2.0	96.9%
7	92.3 \pm 13.5	61.8 \pm 14.2	67.0%
		Mean	109.8 \pm 41.3%
<u>TOTAL ANTRECTOMY</u>			
2	137.7 \pm 38.8	154.4 \pm 23.4	112.1%
3	87.7 \pm 32.2	105.0 \pm 30.1	114.0%
9	100.4 \pm 28.0	112.0 \pm 10.7	111.6%
10	218.2 \pm 43.7	170.1 \pm 45.8	78.0%
		Mean	103.9 \pm 15.0%

TABLE II, 5

acid output in the total antrectomy group was to $38.8 \pm 14.1\%$ for the two-hour output. The corresponding values for subtotal antrectomy were $68.1 \pm 45.2\%$ (Table II, 4). Removal of the dog No. 1 from the latter group brings the corresponding value to $48.7 \pm 25.7\%$.

Further examples of graphs showing the acid responses of animals in each group in both phases of the experiment are shown in Appendix IV.

It can be seen that the removal of the dog whose responses were not reduced by resection approximates the mean reductions, but the standard deviations in the subtotal group remain twice as great as in the total group owing to the wide scatter of results among the former. Application of the "t" test to the acid reductions fails to show any significant difference between the two groups.

The control animals gave essentially unaltered responses throughout the period of studies.

The mean recovery of C-14 PEG from the post-resection stomachs was $83.9 \pm 2.3\%$ (Standard Error). This was not significantly different from the recovery from the whole stomach (Table II, 3).

The previous animal and clinical evidence that antrectomy depressed vagally-stimulated gastric secretion has already been outlined. The results presented here suggest that approximately 60%/

60% of the vagally mediated acid response requires the presence of the intact antrum. The same was not shown to be true of the pepsin secretion. The neuro-hormonal pathway is important for acid but pepsin stimulation appears to depend principally upon the direct neural mechanism (Linde, 1954). Gastrin is known to be a weak stimulant of pepsin production (Gregory, 1968).

That the presence of 10 - 20% of residual antrum had such a variable effect upon the secretory response could be interpreted in a number of ways and may be of some practical importance. It indicates firstly that complete antrectomy is the more likely to give a reliable clinical result. Secondly we might ask what role the intestinal phase may play in these results. A number of workers have produced evidence of gastrin-like hormone production in the duodenum (Lai, 1964; McGuigan, 1968; Mutt and Jorpes, 1967; Celestin, 1967). Information about this phase of secretion is sparse but it is probably under hormonal rather than vagal control (Middleton, Kelly, Nyhus and Harkins, 1968). It seems reasonable to conclude that the antral remnant influenced results.

We could surmise that greater or lesser amounts of gastrin were produced in different dogs by similar volumes of antral tissue. Gastrin assay of the antral remnants might have answered this question. Local factors such as gastritis proximal to the anastomosis could in theory influence gastrin production, /

production, and indeed on review of the post-mortem gastric mucosa slight inflammatory changes could usually be made out proximal to the suture line but no attempt was made to quantitate these..

Alternatively it is very possible that the gastrin boundary does not correspond to the mapped parietal cell boundary and the antral measurements were, therefore, not representative in terms of gastrin-producing tissue. The work of McGuigan (1968) and others using immunological methods should allow an early answer to this question.

Finally it is clear that the results of this study have a strong bearing upon the interpretation of the insulin test for completeness of vagotomy. The relevance to human gastric physiology may be illustrated by reference to Hollander's original data (Weinstein, Hollander, Lauber and Colp, 1950) and to similar data emerging from the first 196 cases in a larger series of secretion tests currently under review at the Gastro-Intestinal Unit, Western General Hospital, Edinburgh (Table II, 1). Attention has already been drawn to these data in respect of the neuro-hormonal synergism in acid stimulation (p. 68). The difference in the incidence of positive tests between vagotomy and drainage on the one hand, and vagotomy and resection on the other, is used in the present context to demonstrate that antral resection/

resection profoundly influences the response to vagal stimulation. In some instance the response may be completely abolished. Waddell (1957) and Stempien, Lee and Dagradi (1968) have noted negative insulin tests in patients who had partial gastrectomy alone. Similar cases have been observed in the Edinburgh series. As noted at the beginning of the discussion, this is not a new observation but it is one that many authors choose to ignore in reporting their incidence of complete vagotomy in series which include gastric resections.

After vagotomy with resection a negative response cannot be assumed to indicate complete vagotomy and even the most trivial response may represent a positive test. Conversely a positive test after vagotomy and resection undoubtedly means intact vagal fibres but it may mean more than that; it may indicate either that antral as well as vagal resection is incomplete or alternatively that residual vagal fibres are capable of direct stimulation of acid release after this procedure in some individuals but not in others. The latter interpretation would tend to support the view that patients differ in the relative dominance of their neural and humoral components of secretion.

P A R T I I I

THE INSULIN STIMULATION

o f

GASTRIC SECRETION

CHAPTER 9INTRODUCTION

The current dominance of vagotomy in the surgery of duodenal ulcer, together with the recognition that inadequate vagotomy predisposes to recurrent ulcer, focuses our attention upon tests of vagal function. Gastric tests of this type may be divided into those applied at operation and those which may be used pre- or post-operatively. Despite the claims of several workers (Burge and Vane 1958; McKibben and Naylor 1962), no reliable operative test is yet available and this field is not discussed further.

It is the purpose of this section to analyse post-operative tests of vagally mediated gastric function in respect of their performance, reproducibility and interpretation.

The Effects of Insulin upon Gastric Secretion

Although earlier workers had recognised the gastric secretory effect of insulin hypoglycaemia, this phenomenon was first advocated as a post-operative test for vagal integrity by Hollander and his associates in 1946.

The Hollander test, as originally described, consisted of the determination of the acid content of gastric aspirate obtained during the two hours after intravenous injection of 15 units of soluble/

soluble insulin. A test was described as positive if, during the two-hour collection, there was a rise of 20 m.Eq./l. or more above basal levels; or a rise of 10 m.Eq./l. if the basal juice was anacid.

In the past ten years, dissatisfaction with these criteria has been voiced. Several workers have suggested other criteria to define a positive response to insulin, taking into consideration such factors as volume increases after insulin (Waddell, 1957), basal secretion values (Bachrach, 1962) and the timing of the response in relation to the insulin injection (Ross and Kay, 1964). More recently Bank, Marks and Louw (1967) have suggested that an analysis of multiple criteria may give a more accurate assessment of the completeness of vagotomy, and their findings have gained support from the data of Gillespie, Gillespie and Kay (1968).

Our present difficulties in interpreting Hollander tests stem in part from the complexity of the physiological response to hypoglycaemia. The rise in production of acid and pepsin by the stomach is the end result of conflicting forces of stimulation and inhibition.

The Stimulation of Secretion by Insulin

Stimulation of secretion is known to be effected via the central nervous structures governing parasympathetic activity.
The/

The evidence has been fully reviewed by Bachrach (1963). Other hypoglycaemic agents such as Tolbutamide have a similar effect (Stempien, Lee and Dagradi 1968). A newer agent, 2 Deoxy-D-Glucose, which blocks intracellular glycolysis, is believed to stimulate by a similar mechanism without producing systemic hypoglycaemia (Hirschowitz and Sachs 1965).

It is established that at the gastric level the secretory mechanism is of a dual nature. Vagal impulses liberate gastrin from the antrum and excite the fundic glands independently. The evidence for this has been reviewed earlier (Part II, Chapters 5 and 6).

Insulin-induced secretion does not begin until a substantial fall in blood glucose has occurred. There is thus a time lag of 15 - 30 minutes.

The critical level of hypoglycaemia required was held by Hollander to be 50 mgs.%. Although it is correct that insufficient hypoglycaemia fails to yield a secretory response (Babkin 1930; Roholm 1930; Hollander 1948), this level is somewhat arbitrary and appears to have been based largely on animal studies. Data will be presented to show that in humans copious secretory responses may be obtained with lesser falls in blood sugar, and indeed Hollander (1946) acknowledged that the critical factor may be rate rather than level of fall.

Numerous/

Numerous studies have shown that the nadir of the hypoglycaemic response to a moderate dose of insulin (15-20 units) falls between 15 and 45 minutes. The rate of return to normality varies with the dose of insulin used (Fig. III, 1).

The secretory response usually begins in the second 15 minutes after the intravenous administration of insulin. It will be shown that the pattern of the curve and the rate of return towards basal levels is influenced, in the experimental animal, by the dose of insulin. Adequate dose-response studies in man are not yet available. With doses of the order of 0.1 - 0.6 units per kg., the acid-pepsin output has generally returned to near-basal levels at the end of a two-hour test.

A second peak occurring after two hours has been described by several groups. In 1953 French, Longmire, Porter, and Movius reported that electrical stimulation of the anterior hypothalamus in monkeys evoked a rise in gastric secretion which could be prevented by vagotomy but not by adrenalectomy, whereas stimulation of the posterior hypothalamus resulted in a delayed secretion which could be prevented by adrenalectomy but not by vagotomy or by section of the cervical cord. They reported further that stimulation by insulin hypoglycaemia followed a pattern similar to that of electrical stimulation, i.e. abolition of the early phase by vagotomy and of the late phase/

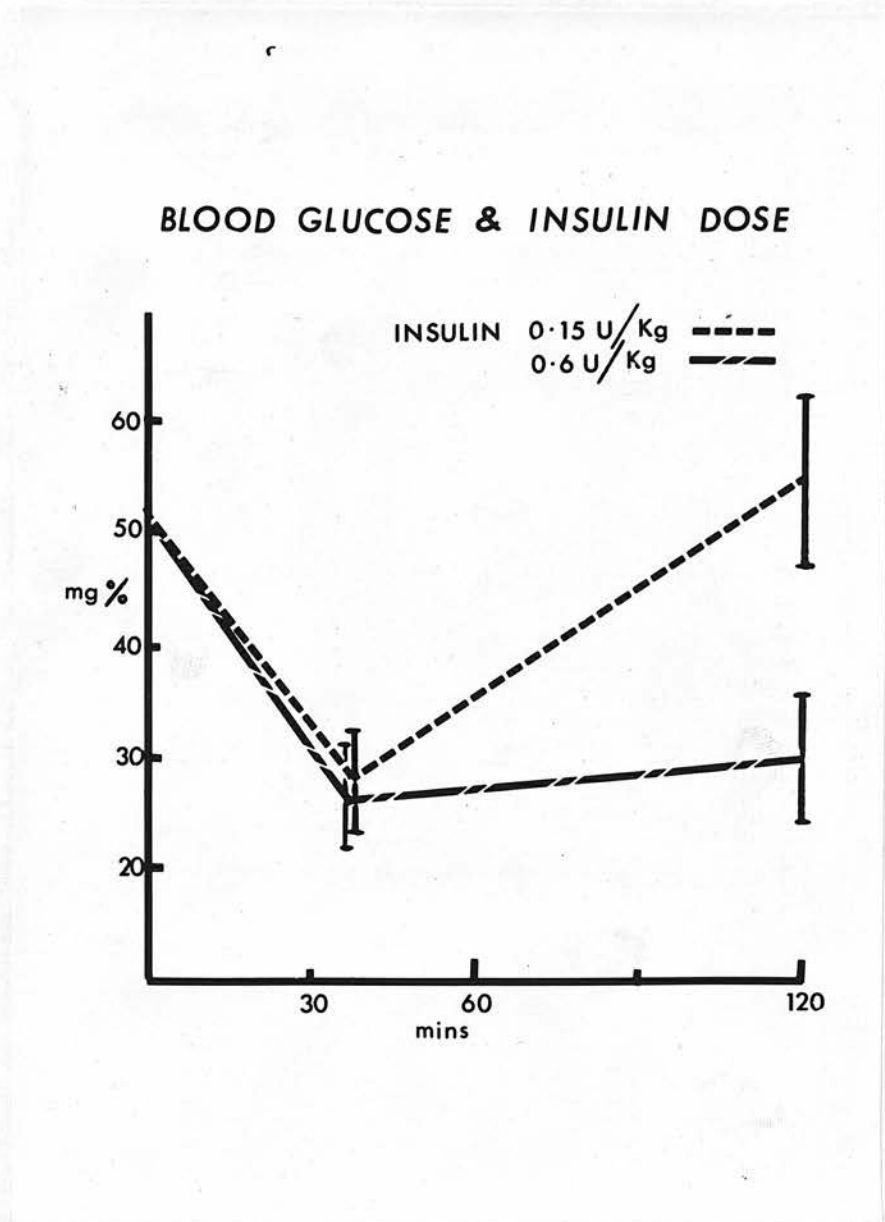


Fig III, 1. The effect of different doses of insulin (0.15 and 0.6 u/kg) upon blood glucose concentration. Means with standard deviations, from 404 secretion tests in 18 dogs.

phase by adrenalectomy. The authors construed these observations as evidence that the first two hours of the secretory response are mediated by the vagus and the second two hours by a pituitary-adrenal hormonal mechanism. In subsequent publications by the same group, the delayed response in humans was not nearly as marked as that shown in monkeys (Stempien, French, Dagradi, Movius and Porter 1958).

Contrary evidence in human subjects has been provided by Sun and Shay (1960) who concluded that intact vagus was necessary for a full delayed response. Further studies in monkeys (Smith, Brooks, Davis and Rothman 1960; Cammock, Nyhus and Harkins 1963) and in dogs (Robbins, Morros, Powell and Hirschowitz 1962; Davis and Brooks 1962) have provided conflicting data. Evidence derived from innervated and denervated gastric pouches in dogs, in which it was shown that antrectomy abolished the late phase and that the latter could not be correlated with plasma cortisol levels led Sircus and co-workers (1963) to conclude that an intact antral-gastric mechanism was necessary for the delayed phase. The role of the pituitary-adrenal axis remains obscure.

It is necessary to draw a clear distinction between the 'delayed response' occurring later than two hours in the animal or human with intact vagi and the 'late positive response' described by Ross and Kay (1964) as sometimes occurring in the post-vagotomy/

post-vagotomy patient.

The positive post-vagotomy responses to insulin are divided by these authors into two groups: the 'early' and 'late' positive responses, the peaks of which fall before 45 minutes and between 45 and 120 minutes after insulin. An early response is attributed to the presence of an intact main vagal trunk and is associated with a higher post-operative maximal acid output (to histamine or pentagastrin) and a greater likelihood of recurrent ulceration; a late response represents small residual vagal fibres and relates to a smaller post-operative maximal acid output and a lower incidence of recurrent ulcer. A recent series of studies involving electrical and insulin stimulation of the vagi in dogs and rats (Pritchard, Griffiths and Harkins 1967; Pritchard, Griffiths and Harkins 1968; Legros and Griffiths 1968) suggests that this anatomical explanation is correct.

The Inhibition of Secretion by Insulin

When the vagus nerves are intact, the excitatory effect of insulin or other vagal stimulants upon gastric secretion greatly exceeds the inhibitory effects during the first two hours after application of the stimulant. When the gastric branches are entirely divided, the secretory response is abolished. It is in the intermediate group, where there is incomplete interruption of/

of the vagal path that difficulty arises in clinical practice, and it is here that the inhibitory effect of insulin may become important.

There is evidence that there are at least two phases of inhibition. The first, when present, occurs within the first 30 minutes of the injection of insulin. The curve of inhibition parallels the fall in blood sugar (Olson and Necheles 1955) and has been attributed to a direct action upon the gastric mucosa, namely deprivation of available carbohydrate substrate in the metabolically active cells (Forrest and Code 1954). Some gastric acid production still occurs however even with massive doses of insulin, such as were used for insulin shock therapy e.g. 95 - 310 units subcutaneously (Sharick and Campbell 1951).

The effect of glucagon provides an alternative explanation. It has been pointed out by several workers, including Dreiling and Janowitz (1959) and Melrose (1960), that glucagon inhibits basal and histamine-stimulated gastric secretion. Standard commercial preparations of insulin contain glucagon. Aylett (1961) demonstrated that the use of glucagon-free insulin might avoid the inhibitory effects but this was not confirmed by Eisenberg, Woodward, Quintana and Dragstedt (1963) who demonstrated a period of inhibition after insulin in dogs despite the use of a glucagon-free preparation.

It/

It is of interest that the inhibitory effect of insulin upon histamine-induced secretion can be entirely reversed by injection or infusion of potassium chloride (Hirschowitz and Sachs 1966).

Insulin is known to lower the level of serum potassium by promoting entry of the ion into cells (Zierler 1959). The direct inhibitory action of insulin appears to be related to its interference with ionic flux and membrane potential in the secreting cell, possibly by altering the distribution of intracellular potassium (Kemp, Herrera, Tsukamoto and Eisenberg 1968).

There is some evidence that a second and later inhibitory effect may operate in response to hypoglycaemia. It is generally recognised that the unpleasant symptoms of hypoglycaemia - sweating, headache, pallor, dizziness, etc. are brought about by release of adrenalin and possibly also noradrenalin into the circulation.

Elevated blood levels of adrenalin in animals and man after the intravenous injection of insulin have been demonstrated by several groups (Bachrach 1963). These agents have been shown to inhibit histamine-stimulated and basal gastric secretions in dogs (Forrest and Code 1954) and to inhibit secretion promoted/

promoted by peptone broth, histamine and insulin in humans (Leonsins and Waddell 1958). Pressor amines, like many other inhibitors, probably reduce gastric secretion by their action on the submucosal vessels (Jacobson 1965). It is postulated that this may be the mechanism which depresses the secretory responses to larger doses of insulin, an effect which is shown in the data of Hirschowitz and O'Leary (1964) and in the animal studies presented in the next chapter.

Thus the inhibitory component of insulin's action undoubtedly exists although the mechanism remains obscure. Its presence suggests the hypothesis that the correct dose of insulin is the smallest which will consistently lower the blood glucose level sufficiently to stimulate vagally-mediated secretion.

The following chapters present data on 2 deoxy-D-glucose as a vagal stimulant, on secretory dose-responses to insulin in dogs and in man, on the interpretation of the insulin test by single and multiple criteria, and on the correlations between the results of insulin tests, maximal and basal acid outputs and the clinical status of the patient before and after gastric surgery. It is hoped that these studies will encourage more effective application and better interpretation of the insulin test in post-operative patients.

CHAPTER 10THE INSULIN SECRETION TEST: DOSE-RESPONSE STUDIESIN DOGS AND IN HUMANS

Although it is more than twenty years since the insulin secretion test was introduced (Hollander 1946), there is no unanimity upon the correct dose of insulin to be used. Hollander based his recommendations upon animal experiments. Dose-response studies were not performed.

It appears to have been assumed by writers on this subject that the dose of insulin was only significant in that it must be enough to produce a fall in blood sugar below 50 mgs.% at which level an "all-or-none" excitation occurred. Evidence that such was not the case in the dog was provided by Hirschowitz and O'Leary in 1964. These authors summarised their findings as follows:-

"The conclusions from 72 experiments are that the characteristic patterns of both pepsin and electrolyte secretion (H^+ , Na^+ , K^+ and Cl^-) could be related to the dose of insulin The patterns of secretion could best be explained by concurrent stimulation and inhibition of gastric electrolyte secretion with doses of larger than 0.15 u/kg. which/

which is apparently the optimal dose for secretory stimulation in the dog".

It therefore seemed important to confirm these findings and, as a next step, to determine whether gastric surgery other than vagotomy might influence the observed differences in insulin dose response. The latter seemed to be a real possibility because of the synergism of the neural and hormonal pathways. The evidence for this has already been fully reviewed (Part II, Chapters 5 and 6). Since many of our gastric surgical patients were being evaluated by insulin secretion tests after vagotomy combined with antrectomy it was decided to determine whether antrectomy alone, by removal of one of the synergistic components, might also alter the pattern of dose-sensitivity to insulin. The effects of total and subtotal antrectomy upon acid and pepsin gastric secretion in dogs have been described in Part II, Chapter 8.

This chapter describes an extension of those studies by the use of widely differing doses of insulin in dogs (Part I) and in humans (Part II).

PART IDOSE RESPONSE IN DOGSMaterials and Methods

Eighteen dogs were prepared with cervical oesophagostomies and gastric cannulae. The method of construction of the cervical cannulae is described in Appendix II. The conduct of the insulin secretion tests and the measurement of acid and pepsin secretion is described in Part II, Chapter 7. The method of estimating gastric recoveries using C¹⁴ polyethylene glycol is described in Appendix III. Blood was sampled for glucose estimation (by the glucose oxidase method) during the basal hour, and at intervals after insulin. The minimum sampling, in every dog was at 35 - 40 minutes and 120 minutes. The two doses of insulin chosen for this study were 0.15 u/kg. body weight - the dose found by Hirschowitz to be optimal in the dog - and four times that amount, 0.6 u./kg.

The data are derived from a total of 404 secretion tests performed by the author on 18 dogs.

Gastric acid and pepsin outputs were studied in two phases. Phase 1 consisted of tests upon the intact stomach (18 dogs). Subsequently, gastric preparations were divided into total antrectomy (6 dogs), subtotal antrectomy (5 dogs) and 4 dogs acted as controls after undergoing pyloroplasty (2) or gastrotomy/

gastrotomy alone (2). Data for each dog in each phase represent the mean of at least three tests. The following parameters were studied with both dose levels:-

- 1) the pattern of the secretory response during the 2-hour post-insulin period.
- 2) the peak $\frac{1}{2}$ -hour output.
- 3) the total 2-hour output.

Dose-Responses to Insulin - The Pattern of Acid Secretion Curves

In response to an intravenous dose of insulin all dogs reached a peak within 15 - 60 minutes. There was a tendency for the peak after 0.15 u/kg. to be higher. One dog (No. 66) consistently failed to show any significant response to 0.15 u/kg. During four tests at this dose level the blood glucose in this animal only fell from a mean basal of 88 mgs.% to means of 59 mgs.% and 61 mgs.% at 45 and 60 minutes respectively. Brisk responses were obtained in this animal to 0.6 u/kg. and means of 47 mgs.% at 45 minutes and 51 mgs.% at 60 minutes were obtained.

The higher dose of 0.6 u/kg. provoked a response with a typically lower initial peak, a period of inhibition occurring at approximately 60 minutes and a second peak (11 dogs) at approximately 90 minutes. With this dose seven dogs maintained higher acid output during the second hour than with the lower dose./

dose. An illustration of these trends in one dog (No. 440) is shown in Figure III, 2.

The mean blood glucose levels at zero time, 45 and 120 minutes in response to the two doses are shown in Figure III, 1. One dog (No. 93) developed epileptiform hypoglycaemic fits on several occasions which necessitated the administration of intravenous glucose.

The means of the responses to the two doses are shown in all 18 dogs in Figure III, 3. It is evident that although individual dogs differed widely in their pattern of secretion the general trends described above can still be detected.

Illustrations of the responses summarised above are presented in Appendix IV.

As reported in Part II, Chapter 8, insulin-stimulated secretion was reduced by a mean of approximately 60% by complete antrectomy and 30% by subtotal antrectomy in this study.

Such reductions appeared to affect the responses to both doses to approximately the same extent and the patterns observed with the whole stomach could not be definitely seen although there was some suggestion in 3 dogs of a more sustained output in the second hour with a higher dose. Representative graphs from this phase of the study are illustrated in Appendix IV.

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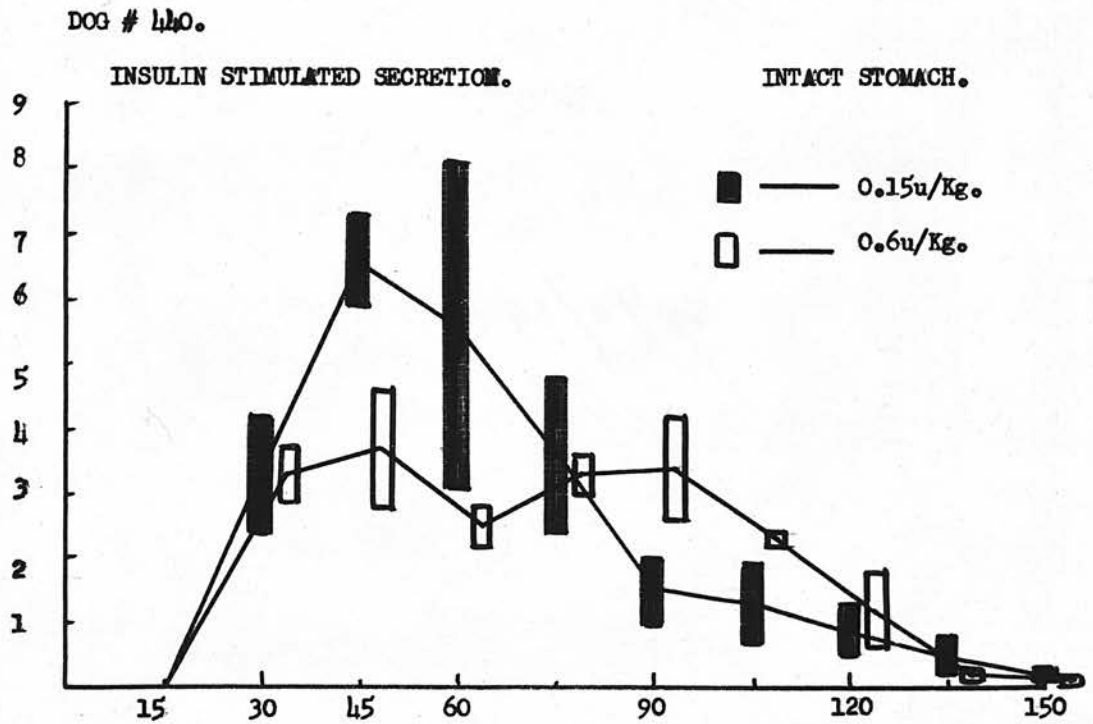


Fig III, 2. Acid responses to 0.15 and 0.6 u/kg insulin.
Means of four tests at each dose level with one
standard deviation above and below the mean.

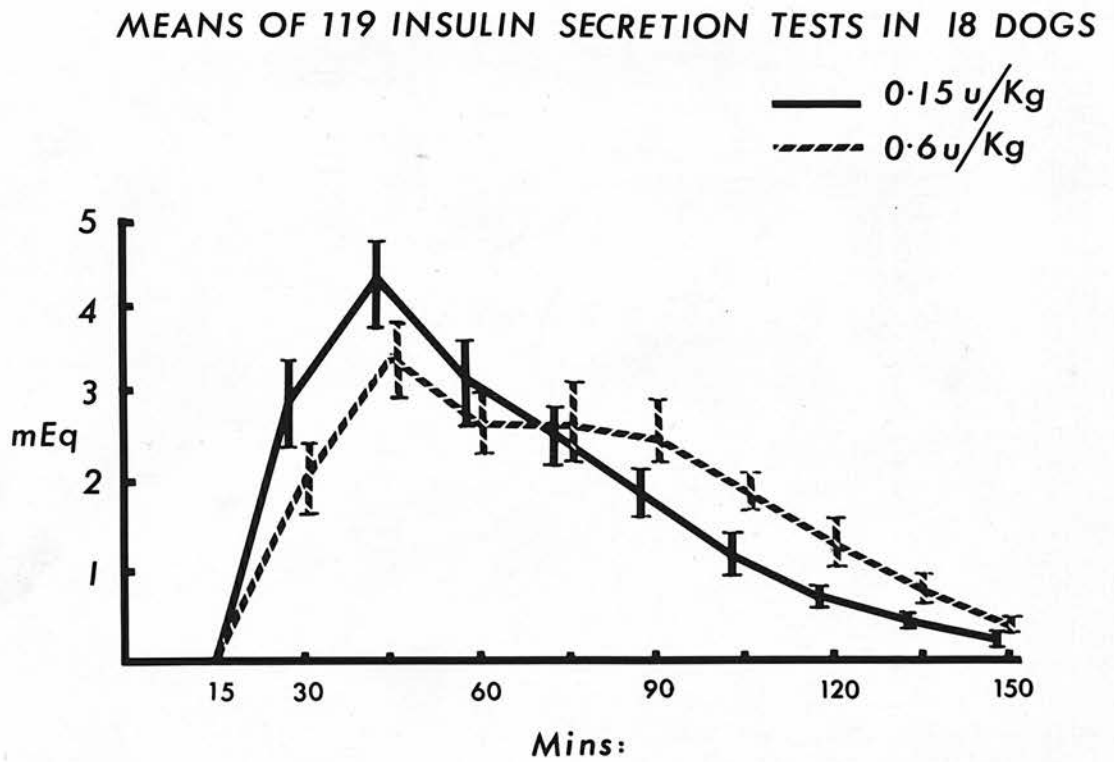


Fig III, 3. The acid secretory response to insulin.
0.15 and 0.6 u/kg in the dog.

The Peak Half-Hour Acid Output

The acid response in the two highest, adjacent 15 minute collections is expressed as the "peak half-hour" output.

Table III, 4 shows the results. Dog No. 66 which failed to achieve satisfactory hypoglycaemia to 0.15 u/kg. has been excluded.

The mean peak half-hour response to 0.15 units was $9.4 \pm$ S.E. 1.3 m.Eq. The response to 0.6 units was $6.9 \pm$ S.E. 0.8 m.Eq. Assessed by the Student 't' test for paired samples these two groups were significantly different ($p = 0.001$).

The Two-Hour Acid Output

Table III, 5 compares the two-hour acid responses to the different doses in 17 dogs. Ten dogs produced a higher mean output after 0.15 u/kg., and the remaining 7 showed a higher mean response to 0.6 u/kg. The means of the entire group to the two doses were $18.9 \pm$ S.E. 2.6 m.Eq. and $17.3 \pm$ S.E. 2.8 m.Eq. respectively. These were not statistically different ($p = > 0.05$).

The Peak Half-Hour and the Two-Hour Acid Outputs after Gastric Resection

The peak half-hour and two-hour acid outputs in Phase 2 of the study in 10 dogs were examined for differences in dose-response. The results are shown in Table III, 6.

The/

PEAK $\frac{1}{2}$ -HOUR INSULIN-STIMULATED ACID OUTPUT
FROM THE WHOLE CANINE STOMACH

(17 DOGS)

Dog No.	0.15u/kg m.Eq. \pm S.E.	0.6u/kg m.Eq. \pm S.E.
1 20	3.0 \pm 0.4	4.2 \pm 0.6
2 31	3.0 \pm 0.6	3.3 \pm 0.5
3 68	17.1 \pm 0.9	13.7 \pm 0.9
4 80	6.5 \pm 0.6	4.8 \pm 0.5
5 87	8.5 \pm 0.8	3.9 \pm 0.4
6 116	12.0 \pm 1.2	6.8 \pm 0.9
7 93	14.8 \pm 0.9	9.0 \pm 1.2
8 149	16.9 \pm 0.7	13.7 \pm 0.7
9 156	4.1 \pm 0.3	3.8 \pm 0.7
10 417	8.7 \pm 0.7	7.0 \pm 0.8
11 199	9.9 \pm 1.8	8.4 \pm 1.0
12 209	6.8 \pm 0.6	3.3 \pm 0.5
13 219	5.7 \pm 0.6	4.0 \pm 0.6
14 368	7.9 \pm 0.8	7.4 \pm 0.8
15 375	9.1 \pm 0.8	11.2 \pm 0.6
16 440	12.1 \pm 1.5	7.1 \pm 0.5
17 450	13.5 \pm 0.6	5.0 \pm 0.4
Mean	9.4 \pm S.D. 1.3	6.9 \pm S.D. 0.8

(p = 0.001)

TABLE III, 4

THE 2-HOUR INSULIN-STIMULATED ACID OUTPUT
FROM THE WHOLE CANINE STOMACH

(17 DOGS)

Dog No.	0.15u/kg (m.Eq. \pm S.E.)	0.6u/kg (m.Eq. \pm S.E.)
1 20	4.1 \pm 0.7	5.1 \pm 0.8
2 31	5.7 \pm 1.2	6.1 \pm 1.7
3 68	37.7 \pm 2.7	42.5 \pm 3.3
4 80	13.4 \pm 1.1	12.1 \pm 1.9
5 87	14.7 \pm 1.0	9.7 \pm 0.8
6 116	19.5 \pm 2.1	13.3 \pm 1.5
7 93	27.4 \pm 2.7	20.8 \pm 2.1
8 149	37.0 \pm 3.4	43.0 \pm 3.0
9 156	7.8 \pm 0.8	6.8 \pm 0.9
10 417	14.6 \pm 1.3	15.5 \pm 1.6
11 199	27.6 \pm 2.8	23.5 \pm 2.3
12 209	11.5 \pm 1.5	8.7 \pm 0.9
13 219	8.7 \pm 0.9	8.1 \pm 1.0
14 368	14.8 \pm 1.8	15.4 \pm 1.2
15 375	20.3 \pm 2.5	28.6 \pm 2.3
16 440	22.4 \pm 2.1	20.0 \pm 1.9
17 450	34.1 \pm 3.5	14.8 \pm 1.5
Mean	18.9 \pm S.D. 2.6	17.3 \pm S.D. 2.8

(p = > 0.05)

TABLE III, 5

PEAK HALF-HOUR AND TWO HOUR ACID OUTPUTS AFTER GASTRIC RESECTION

Dog No.	Operation	$\frac{1}{2}$ -Hr. Output		2-Hr. Output	
		0.15u	0.16u	0.15u	0.6u
20	T.A.	1.0	0.5	2.3	1.1
31	S.A.	4.0	2.7	9.3	6.2
68	T.A.	5.1	7.2	9.9	19.0
80	T.A.	1.4	1.8	2.9	3.5
93	S.A.	1.7	1.5	2.7	2.7
149	T.A.	8.9	9.1	16.8	24.0
219	S.A.	2.4	3.4	4.4	5.2
368	S.A.	2.8	2.3	4.7	4.9
440	T.A.	3.7	2.6	9.1	6.5
450	T.A.	3.7	2.8	7.3	5.8
Mean & S.D.		3.0 \pm 2.3	3.0 \pm 2.5	6.0 \pm 4.5	6.8 \pm 6.9

(T.A. = Total Antrectomy
S.A. = Subtotal Antrectomy)

TABLE III, 6

PEAK $\frac{1}{2}$ -HOUR AND 2-HOUR PEPSIN INSULIN-STIMULATED OUTPUTS
IN RESPONSE TO 0.15u/Kg AND 0.6u/Kg BEFORE AND AFTER ANTRECTOMY
IN 10 DOGS

PEPSIN OUTPUTS (Mgs)

	BEFORE ANTRECTOMY		AFTER ANTRECTOMY	
	PEAK $\frac{1}{2}$ -HR. (Mean & S.D.)	2-HOUR (Mean & S.D.)	PEAK $\frac{1}{2}$ -HR. (Mean & S.D.)	2-HOUR (Mean & S.D.)
0.15u/Kg	86.7 \pm 14.5	125.7 \pm 26.6	42.3 \pm 13.3	108.2 \pm 27.1
0.6u/Kg	71.9 \pm 18.4	93.8 \pm 23.3	86.7 \pm 20.7	109.2 \pm 28.2

TABLE III, 7

The differences between the mean outputs in response to the two doses were slight and were not statistically different. Subdivision of the animals into those with and without complete antrectomy also failed to reveal any difference.

Dose Response of Pepsin Secretion

Table III, 7 summarises the findings in respect of pepsin output. No significant difference in pepsin outputs was noted in response to the different doses, either before or after antrectomy. The observation that antrectomy has relatively little effect on vagally-induced pepsin secretion has been discussed earlier (Chapter 8).

Summary

It is acknowledged that differences in individual sensitivity to insulin, which undoubtedly occur, could have been better elucidated had circumstances allowed the construction of full dose-response curves for each animal. Nevertheless this study demonstrates a statistically significant difference between the peak half-hour acid responses of the intact canine stomach to insulin in intravenous doses of 0.15 and 0.6 u/kg.

When the sensitivity of the secreting cells to vagal stimulation was reduced by antrectomy, significant differences in dose response were no longer detectable. No difference in the dose response of pepsin secretion was observed.

PART II

DOSE RESPONSES IN HUMANS

This section constitutes a brief report upon a study of the responses of pre- and post-operative patients to different doses of insulin (0.1 units and 0.3 u/kg.).

Materials and Methods

The method of conducting insulin tests is discussed in Chapter 12. To date 21 patients have been studied. It was explained to each patient that the extra tests were not essential to their management, and their co-operation was obtained. Paired tests were performed within two or three days of each other and in each case both were carried out by the same person; a Staff-Nurse/Technician, a Resident supervised by the author, or the author himself. Only one test at each dose level was performed on each patient in each phase of the study, but four patients underwent both pre- and post-operative studies.

In the case of the 9 post-operative patients the operations were as follows: 1: truncal vagotomy and gastroenterostomy, 3: selective vagotomy and gastroenterostomy, 2: selective vagotomy and pyloroplasty and 3: selective vagotomy and hemi-gastrectomy.

Results

The two doses have been compared in respect of peak 1-hour acid (the sum of the highest three adjacent 20 minute samples) and/

and the peak concentration (highest acid concentration reached during the post-insulin 2 hours) both as separate pre- and post-operative groups and collectively by the Student 't' test for paired samples. The results are shown in Tables III, 8 (a) and (b).

Blood Glucose

The mean blood glucose level at 35 - 45 minutes was 38 ± 6 mgs.% after 0.1 u/kg. compared with 28 ± 6 mgs.% after 0.3 u/kg.

One patient in the latter group became stuporose and was roused by intravenous glucose. His blood glucose levels at 35 and 45 minutes were 10 and 6 mgs.% respectively. The symptoms of hypoglycaemia were unquestionably more troublesome in the higher dose group. The average weight in this series was 65 kgs. The average dose therefore was 19.5 units - less than the 20 units advocated by many groups (p.136). The highest dose given was 23 units to a man of 78 kgs. (W.H.: Tables III, 8 (a) and (b)). He suffered no unusual hypoglycaemic reaction.

Acid Response to Different Doses (Table III, 8 (a))

The mean pre-operative acid concentration was 118 ± 16 after 0.1 u/kg. and 116 ± 20 after 0.6 u/kg. Post-operatively the corresponding values were 50 ± 43 and 38 ± 28 respectively. These differences were not significant either separately or when/

PRE-OPERATIVE	INSULIN 0.1 u/Kg.				INSULIN 0.3 u/Kg.			
	Peak 1-Hr. (m.Eq)	Peak Conc. (m.Eq/l)	Blood Glucose (mg.%)	Multiple Criteria	Peak 1-Hr. (m.Eq)	Peak Conc. (m.Eq/l)	Blood Glucose (mgs.%)	Multiple Criteria
1. W.D.	37	131	35	-	35	133	38	-
2. T.K.	20	118	36	-	20	138	28	-
3. L.D.	43	110	54	-	37	115	36	-
4. W.T.	24	100	30	-	10	86	6	-
5. G.I.	52	139	37	-	45	140	33	-
6. P.J.	52	120	38	-	24	92	30	-
7. J.G.	19	103	24	-	28	94	20	-
8. D.S.	50	138	44	-	54	130	35	-
9. R. McG.	46	128	40	-	33	118	22	-
10. W.H.	9	88	39	-	11	118	30	-
11. A.R.	21	121	52	-	18	120	34	-
	Mean	118+16	38+7	-	Mean	116+20	28+9	-

TABLE III, 8 (a)

PRE-OPERATIVE RESPONSE TO TWO DIFFERENT DOSES OF INSULIN

	INSULIN 0.1 u/kg.				INSULIN 0.3 u/kg.			
	Peak 1-Hr. (m.Eq)	Peak Conc. (m.Eq/l)	Blood Glucose (mg.%)	Multiple Criteria	Peak 1-Hr. (m.Eq)	Peak Conc. (m.Eq/l)	Blood Glucose (mgs.%)	Multiple Criteria
POST-OPERATIVE								
13. D.F.	48.0	138	43	+++++	26.1	121	37	++++
14. L.D.	5.9	55	48	++	1.9	25	32	-
15. D.McN.	1.6	54	39	+	2.2	58	29	+
16. R.B.	8.3	84	33	+++	1.1	36	27	+
17. J.B.	0.0	0	29	-	1.3	20	20	-
18. A.R.	0.5	15	42	+	0.0	0	34	+
19. G.I.	0.6	15	40	-	1.3	21	31	-
20. R.McG.	4.4	71	34	+	4.3	61	19	+
21. A.W.	2.2	21	38	+	0.0	0	23	+
	Mean	50+43	38+6		Mean	38+28	28+6	

TABLE III, 8 (b)

POST-OPERATIVE RESPONSE TO TWO DIFFERENT DOSES OF INSULIN

when the data for each dose were pooled into a single group.

A significant difference did emerge however when the acid output in m.Eq./hr. in both pre- and post-operative groups is compared by the Student 't' test for paired samples ($0.02 < p < 0.05$). Considered as separate pre- and post-operative groups the difference was not significant, the numbers as yet being small.

Of particular interest is patient No. 16, R.B. who in tests performed on successive days approximately two years after selective vagotomy showed a Hollander - positive (3+) response to 0.1 u/kg. while showing a Hollander negative (1+ = volume rise only) response to 0.3 u/kg. insulin.

Discussion

Repeated tests on each patient would have been preferable. The practical objections to this are obvious. Dogmatic statements cannot be made upon the basis of this small study but the results suggest two things. Firstly the lower dose of insulin appeared to be superior in respect of hypoglycaemic symptoms and a significantly greater acid output. Secondly, in patients with weak or borderline responses, because of the proportionately greater inhibitory effect of the higher dose, the difference may be critical and may result in false-negative responses with the latter dose.

Thus the findings tend to confirm the hypothesis (Chapter 9) that/

that the correct dose of insulin is the smallest which will consistently produce sufficient hypoglycaemia to provoke the vagally-mediated response.

Balancing these findings with the observation from our larger series that 4% of patients failed to respond to 0.1 u/kg. the dose chosen for our current clinical testing is 0.15 u/kg. The problem merits further investigation. Dose-response studies in patients who provide equivocal tests would be of great interest.

CHAPTER 112-DEOXY-D-GLUCOSE AS A VAGAL STIMULANT

The search for a vagal stimulant which might avoid the unpleasant side effects of insulin has led a number of workers to describe the use of 2-Deoxy-D-Glucose (2-DG) both in dogs and in humans.

2-Deoxy-D-Glucose has been studied as an inhibitor of cell growth. It interferes with intracellular glucose metabolism, reduces glycolysis and inhibits glucose uptake. It is not an insulin antagonist, does not cause hypoglycaemia and is free of the inhibitory effects upon gastric secretion shown by insulin (Hirschowitz and Sachs 1965).

Duke, Hirschowitz and Sachs (1965) and Thomas and Duthie (1966) have used this substance in humans as a test for vagotomy and found it to be an effective gastric stimulant. It is not yet certain, however, that this drug is sufficiently free from toxic side effects to allow general use (Kay 1969).

During the course of the animal secretion studies described in Chapters 7 and 10, opportunity was taken to examine features of the acid response to this new agent. The careful dose-response studies of Hirschowitz and Sachs (1965) had demonstrated 100 mgs./kg. to produce a maximal response. This dose was therefore used in the following study.

Materials/

Materials and Methods

The preparation of the animals with cervical oesophagostomies conduct of the tests and determination of acid output have been described in Chapter 8 (p. 80). The 2-DG, provided by Sigma Chemical Company, was given by intravenous infusion according to the method of Duke, Hirschowitz and Sachs (1965). An intravenous drip of lactated Ringer's solution was set up and the 2-DG (100 mgs. per kg. body weight) infused over a 10-minute period. Three animals whose responses 0.15 and 0.6 units of insulin per kg. were well established were chosen. Two of these animals had undergone sub-total antrectomy (No's 66 and 93) and one had an intact stomach (No. 199).

Upon completion of studies on the initial responses the three dogs underwent truncal vagotomy and the tests were repeated.

Results

The two-hour and peak half-hour acid responses to 2-DG (100 mgs./kg.) are tabulated with the responses to insulin 0.15 and 0.6 u./kg. in the three animals in Table III, 9.

The graphs (Fig. III, 10) in each instance represent means (with standard deviations) of three tests.

In/

INSULIN AND 2-DEOXY-D-GLUCOSE-INDUCED
ACID SECRETION IN THREE DOGS

Dog No.	Insulin 0.15 u/kg.		Insulin 0.6 u/kg.		2DG 100 mg./kg.	
	Peak $\frac{1}{2}$ Hr.	2 Hr.	Peak $\frac{1}{2}$ Hr.	2 Hr.	Peak $\frac{1}{2}$ Hr.	2 Hr.
66	1.1 \pm 0.1	2.1 \pm 0.2	1.1 \pm 0.1	1.5 \pm 0.2	1.7 \pm 0.4	3.5 \pm 0.6
93	1.7 \pm 0.2	2.7 \pm 0.3	1.5 \pm 0.2	2.7 \pm 0.2	4.0 \pm 0.9	9.6 \pm 1.9
199	9.9 \pm 1.8	27.6 \pm 2.8	8.4 \pm 1.0	23.5 \pm 2.3	10.9 \pm 2.1	30.5 \pm 4.7

TABLE III, 9

THE ACID RESPONSE TO 2-DEOXY-D-GLUCOSE (100mgs/Kg)

AND TO INSULIN (0.15 & 0.6 u/Kg) IN 3 DOGS

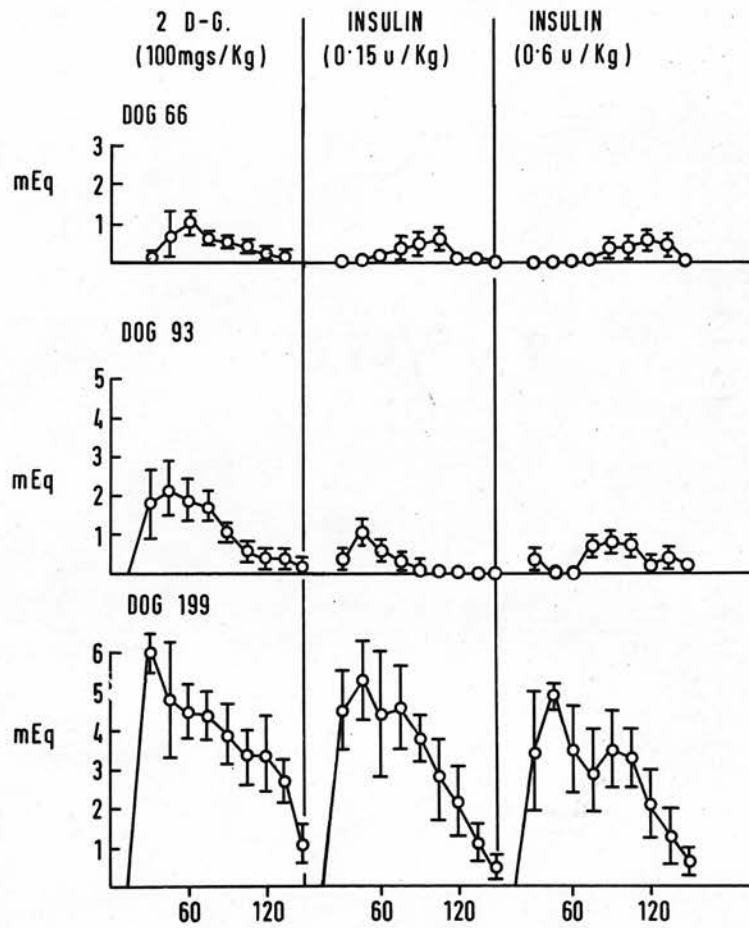


FIGURE III, 10.

In all three animals, whether compared by two hour or half hour responses, the output after 2-DG was greater than that after either dose of insulin. It is of interest that dog No. 93 which on several occasions developed epileptiform hypoglycaemic fits in response to insulin, 0.6 u./kg., also did so in response to 2-DG, 100 mgs./kg., despite the fact that no hypoglycaemia occurred with the latter stimulant.

The pattern of the 2-DG-stimulated responses showed a peak occurring in the second or third 15 minute period and a fall-off of stimulation which appeared to be more gradual than that following the peak of insulin 0.15 u./kg. (Fig. III, 10).

Truncal vagotomy abolished the response to 2-DG in all three dogs.

Discussion

Dose response studies using a range of doses of insulin and 2-DG would be mandatory in order to compare these two stimulants fully. Exigencies of time and facilities did not allow this approach. The following conclusions may, however, be drawn from this limited study.

It is confirmed that 2-DG is a potent stimulant of gastric secretion both in the intact stomach and after sub-total antrectomy. The 2-DG-induced response is abolished by vagotomy. The timing of the response, in the dose used, resembles that of/

of insulin, 0.15 u./kg., with a peak occurring between 15 and 45 minutes after infusion of the stimulant. No hypoglycaemia occurred, but the occurrence of epileptiform seizures identical to those of insulin hypoglycaemia suggests that the intracellular mechanism in the central nervous system which is influenced by the two substances is probably the same.

It might be expected that since 2-DG is free of insulin-like inhibitory effects it should be capable of producing a response equal to the maximal histamine or pentagastrin response. Tests of maximal histamine or pentagastrin-stimulated acid output were not a part of this study, but the data of Hirschowitz and Sachs (1965) indicate that this is in fact the case.

CHAPTER 12INSULIN, HISTAMINE AND PENTAGASTRIN-STIMULATED
ACID AND BASAL ACID MEASUREMENTS BEFORE VAGOTOMY

It is proposed in this chapter to discuss certain aspects of the response of the un-operated human stomach to insulin.

It has been made clear in foregoing chapters why the dose of insulin may be critical. Judging by the work of previous authors a generous choice is available.

Doses used in human gastric secretion tests have ranged through a variety of arbitrary fixed dosages such as 25 units (Olson and Necheles 1955), 20 units (Hunt 1950, Lythgoe 1961, Bell 1963, Ross and Kay 1964, Gillespie, Gillespie and Kay 1968), 15 - 20 units (Bank, Marks and Louw 1967), 15 units (Hollander 1946, Drawiec, Straughn and Polish 1965), 12 - 15 units (Waddell 1957) and 11 units (Stempien, Lee and Dagradi 1968).

Other authors have sensibly adjusted the doses in accordance with body weight; 0.25 - 0.3 u/kg. (Sun and Shay 1960), 0.15 u/kg. (Hubel 1964). One outcome of these differences is that it becomes unsatisfactory to attempt comparisons between the results from different centres.

The following points are pertinent in choosing a suitable dose for routine clinical use:-

1./

1. An adequate fall in blood sugar to approximately 50 mgs.%, or below, is required. This level was arbitrarily chosen by Hollander (1946). While it is true that a substantial fall in blood sugar is necessary we have recorded a number of strongly positive tests where this particular level was not reached.
2. The symptoms of hypoglycaemia are unpleasant. Unnecessarily low levels of blood sugar should therefore be avoided.
3. The inhibitory effects of insulin; the evidence for which and probable effect on the post-vagotomy response have been outlined in Chapters 9 and 10.

For the past ten years it has been the practice at the Gastro-Intestinal Unit, Western General Hospital, to carry out insulin tests both before and after operation. The insulin tests reviewed in this thesis, with the exception of those reported in the dose-response study, were performed with an exceptionally low dose of insulin, namely 0.1 u/kg.

Pre-operative insulin tests have now been discontinued but the data already obtained provides interesting and probably unique information on the effect of this small dose upon the un-operated/

un-operated human stomach. Correlations with histamine and pentagastrin maximal acid output (M.A.O.) tests have also been studied.

Materials and Methods

Pre- and post-operative tests conducted during the last ten years have been studied in 344 patients treated surgically for duodenal ulcer. A small number of these patients underwent operation more than a decade ago but their tests were performed more recently. All these patients were treated by the operation of vagotomy, either truncal (222) or selective (122). The vagotomy was combined with a drainage procedure (gastroenterostomy or pyloroplasty) in 243, with partial gastrectomy in 103 and without any accompanying procedure in 7 patients.

The majority of these secretion tests were conducted by specially trained staff nurse-technicians. A small proportion were conducted by ward residents or by the author during the course of follow-up studies of selective vagotomy. Conduct of the tests has been in almost all respects the same throughout the period of study.

Two variations which have appeared from time to time during this period are changes in the times of sampling gastric juice after insulin and the use of combined M.A.O. and insulin tests.

In the majority of tests the two hours after insulin have been/

been divided into six 20 minute samples and this is the present practice. Some however have comprised four 30-minute samples. For a period in 1963-64 combined M.A.O. and insulin tests were performed. In the majority of instances the I.S.T. was performed first and was therefore suitable for inclusion and group analysis. I.S.T.'s performed one to two hours after histamine stimulation have been excluded from the group because of failure of acid concentrations to fall to basal levels even two hours after histamine. M.A.O.'s performed as the second half of a combined test are also excluded. There may be a place for this type of combined test but interpretation must differ from that applied to the I.S.T. in isolation.

The Maximal Acid Output (M.A.O.)

The theoretical basis for tests of maximal acid output is well known. A direct stimulant such as histamine, histalog or pentagastrin is given in a dose sufficient to provoke a response which is proportional to the parietal cell mass (Card and Marks 1960).

A modification of Kay's augmented histamine test (1953) has been the form of M.A.O. preferred in this unit until 1967 when pentagastrin was substituted as the stimulant. For the purposes of this analysis it is assumed that a subcutaneous dose of/

of 6.0 ug./kg. pentagastrin elicits a similar response to 0.04 mgs./kg. histamine subcutaneously (Multicentre Trial 1967). The term "maximal" is defined for our purposes as representing the highest acid output capable of being produced by a subcutaneous dose of these stimulants.

The M.A.O. test has been conducted as follows. The patient, after an overnight fast, is intubated with a radio-opaque Levine tube which is screened into position in the gastric corpus. He is then placed in the left lateral position, or whichever position provides the most free drainage of juice, and gastric aspiration is commenced by complete aspiration of the fasting juice. Continuous vacuum aspiration is then continued through the "basal hour", at the end of which the stimulant, histamine 0.04 mgs./kg. or pentagastrin (Peptavlon, I.C.I.) 6.0 ug./kg. is given subcutaneously. Histamine requires the prior administration of an antihistamine such as mepyramine maleate (Anthisan) 50 mgs. intramuscularly to counter its uncomfortable vasomotor effects. The post-stimulant secretion is collected for one hour in three 20-minute samples. The vacuum pump is maintained at a negative pressure of 3 - 5 cm.Hg. and frequent checks of the patency of the tube by hand-syringe are essential.

The/

The Insulin Test

The preparation of the patient and techniques of aspiration are the same as for the M.A.O. test.

Until 1969 the dose of insulin used in the Unit has been 0.1 u/kg. soluble insulin. This year, as a result of the studies outlined in this thesis doses of 0.2 units and 0.3 u/kg. have also been used in a number of patients. Current practice is to use 0.15 u/kg., a sliding scale for which is shown in Appendix V.

It has not been routine practice in this series of insulin tests for blood glucose samples to be monitored. One reason for this economy becomes apparent upon reviewing the results of the pre-operative insulin tests which were available as controls for the post-operative response, namely a satisfactory response in 96% of patients.

Since it is no longer our policy to conduct control pre-operative insulin tests a return to the practice of estimating blood sugar during the basal hour and between 35 and 45 minutes after insulin has been made. Blood glucose data are therefore available for the more recent tests only.

Determination of Acid

Aliquots of gastric juice are titrated against N/10 Sodium Hydroxide. Titrations have evolved through the measurement/

measurement of "free" and "total" by the use of Topfer's reagent (only "total" acid being documented in this analysis) and the use of phenolphthalein to titrate "total" acid only - both by manual burette titration - to the current method using an automatic, electronically-controlled titrator, (Radiometer Copenhagen) titrating to pH7.

Acid output in milliequivalents per unit time is determined by multiplying volume of gastric juice by titrated concentration.

Results

The characteristics of the insulin - stimulated acid response of the intact human stomach discussed here are as follows:-

- (1) the peak one-hour acid output compared
with the one-hour M.A.O.
- (2) the highest concentrations of acid
reached.
- (3) the rise of acid concentration after
insulin above the highest recorded
basal concentration.

Available for study are 194 pre-operative insulin tests.

Twenty-two involved the use of doses other than 0.1 u/kg. and these are discussed under a separate heading (Part II, Chapter 10).

Of the 171 tests using 0.1 u/kg. 6 are rejected as failing to show a rise of 20 m.Eq. or more above the highest basal concentration/

concentration thus giving a false negative response rate of 3.8%. The relevant concentrations are shown on the following table.

Table III, 11: Failed Insulin Tests

<u>Patient No.</u>	<u>Peak I.S.T. Conc. (m.Eq./l.)</u>	<u>Highest Basal Conc. (m.Eq./l.)</u>
7	43	71
20	96	83
45	70	55
183	40	27
272	54	84
311	77	66

The remaining 165 have been analysed by comparing the peak 1-hour insulin response with the 1-hour M.A.O.

Comparison of Maximal Acid Output with Insulin-Stimulated Output

Of the 344 patients studied 30 had undergone emergency surgery and therefore pre-operative secretion tests were not available. Pre-operative M.A.O.'s were available in 314, of which 247 were histamine-stimulated M.A.O.'s and 67 were pentagastrin M.A.O.'s. First the results with these two stimulants were tested for comparability. The mean one-hour outputs of the two were $40.3 \pm$ S.D. 7.3 m.Eq. and $40.4 \pm$ 7.0 m.Eq. respectively. No significant difference is detectable between these two means. This finding, together with the results/

results of the "Multicentre" Trial, (1967), is taken as justification for considering the histamine M.A.O.'s together with the pentagastrin M.A.O.'s as an homogeneous group.

As a method of comparing the M.A.O. and I.S.T. the 'peak 1-hour' response (that is defined as the sum of the highest three adjacent 20-minute collections) of the latter was expressed as a percentage of the former. In 160 patients pre-operative M.A.O.'s and I.S.T.'s were available which appeared to be technically satisfactory. For each pair the 'peak 1-hour' I.S.T. was calculated as a percentage of the 1-hour M.A.O. The mean of these percentages was $85.4 \pm \text{S.D. } 16.1$.

The highest concentration of acid obtained, expressed as a per cent ratio in the same way, showed a mean of $97 \pm \text{S.D. } 17.6\%$. The mean peak M.A.O. concentration was $125.3 \pm \text{S.D. } 17.2 \text{ m.Eq./l.}$. The mean peak I.S.T. concentration was $121.4 \pm 16.7 \text{ m.Eq./l.}$

Analysis of the difference in concentrations by the Student 't' test for paired samples shows the difference to be statistically significant ($p = 0.001$).

Since the ratio of 1-hour acid output (m.Eq./hour) of I.S.T. to M.A.O. had a mean of 85% while that of concentration was 97% it follows that the mean volume of gastric juice was also greater in response to histamine or pentagastrin than to insulin.

In this pre-operative series the mean basal concentration of acid, taking the highest value obtained where more than one basal/

basal hour was collected, was $49.2 \pm$ S.D. 7.0 m.Eq./l. The mean basal output was $5.2 \pm$ S.D. 0.9 m.Eq./hour.

DISCUSSION

Hydrochloric acid in gastric juice does not behave like a pure solution owing to the buffering action of mucus and small amounts of weak un-ionised acids. There is some disagreement as to the relative merits of pH-measurement and titration methods and also about the appropriate pH to which titration should be carried; (Moore and Scarlata 1965, Lubran 1966, Grossman 1966, Moore 1968). The range of acid concentrations recorded in the M.A.O.'s, 61 - 147 m.Eq./l., suggests a probable minimum error of 18% at the uppermost end of the scale since acid of strength greater than 0.1 N HCl is not generally recorded in gastric juice and this represents a pH of approximately one or a concentration of 129 m.Eq./l. This discrepancy is not entirely observer-error since, as respective titration curves for gastric juice and pure HCl show, the buffering action in the juice results in over-estimation of its HCl content (Lubran 1966).

Although during the accumulation of cases in this series the methods of titrating gastric juice have become more accurate it is felt that the differences are slight enough to allow analysis as a single group.

The/

The principal findings can be summarised briefly as follows:-

- (1) In 96% of patients in whom the vagus nerves and stomach were intact a dose of 0.1 u/kg. insulin provoked a vigorous positive response.
- (2) This response, expressed as a peak 1-hour output, averaged 85% of the 1-hour M.A.O.
- (3) The lower peak 1-hour response to insulin is the result both of lower volumes and lower concentrations of acid in the aspirated juice.

It can only be stated from this data that histamine or pentagastrin are more potent stimulants than insulin as measured over one hour and in the doses used. It is likely that this difference is a measure of insulin's inhibitory component, since the vagal pathway, when stimulated by 2-deoxy-D-glucose is capable of producing a response comparable to the maximal histamine response both in animals and in man (Duke, Hirschowitz and Sachs 1965). The critical experiments in humans involving dose-response studies, sampling at more frequent intervals and simultaneous measurement of gastric recoveries using a non-absorbable marker, which would allow accurate determination of maximal secretory rate in response to insulin, have not yet been done.*

It/

*See end of chapter for addendum

It is concluded that insulin 0.1 u/kg. is a potent gastric stimulant. This dose fails to produce adequate hypoglycaemia in approximately 4% of cases. Thus, we must be prepared either to monitor blood glucose levels carefully or to use a slightly larger dose. Appendix V. shows a suitable sliding scale of 0.15 u/kg. for clinical use.

*Addendum

Since this chapter was prepared M. I. Grossman has reported to the American Gastroenterology Association (1969) upon dose-response studies in 5 non-operated subjects. He found 0.2 units/kg. body weight insulin to be the optimal dose but did not use a dose intermediate between 0.1 and 0.2 units/kg. body weight.

CHAPTER 13INTERPRETATION OF THE INSULIN TEST II: RATIONALE AND ELIMINATION OF UNRELIABLE TESTS

In the foregoing chapter the characteristics of the insulin response (I.S.T.) in the intact stomach are discussed. Attention is now turned to the test in its more important clinical setting, that is as a post-operative test of vagal integrity.

Even when a satisfactory form of test has evolved and the correct dose of insulin is determined, experience and patience on the part of the individual conducting the test are required if an I.S.T. - or any gastric secretion test, - is to be reliable. Given all these pre-requisites the clinical value of the test may be yet diminished by uncertainty as to its interpretation.

Hollander's criteria of a positive test have been outlined in the introduction to this section (Chapter 9). Their weakness lies partly in that the concentration of the basal acid is used as the point of reference. It is concluded, as a result of analysis of secretion tests in 344 patients that the collection of gastric juice which has most often proved suspect or clearly faulty has been that of the basal juice. The/

The commonest reason for this has been failure to remove gastric fasting juice completely, prior to collection of the basal hour. Any gastric stasis or duodeno-gastric or jejuno-gastric reflux has a disproportionate effect on basal juice whose volume and acid content is usually low. A possible solution is to collect more than one basal hour. This adds to what is already a long and uncomfortable test.

Presented below are examples of late post-operative insulin tests which have given rise to clinical uncertainty when interpreted by Hollander's criteria.

Example 1. - W.C. (Selective Vagotomy & Pyloroplasty 24.8.64)

I.S.T. 13/3/66

<u>Time</u>	<u>Volume</u> (mls.)	<u>Conc.</u> (m.Eq./l)	<u>Output</u> (m.Eq.)	<u>Blood Glucose</u> (mgms.%)
Basal	165	50	8.3	82
0-20'	10	64	0.6	
20-40'	8	62	0.5	
40-60'	5	54	0.3	39
60-80'	22	62	1.4	
80-100'	23	66	1.5	
100-120	27	66	1.8	
<hr/>				
6.1 m.Eq./2 hrs.				

Comment: The basal collection is clearly faulty due to failure to evacuate the fasting juice. In addition the concentrations of 54-66 mgms.% are abnormally high for complete vagotomy, as is an output of 4.7 m.Eq./

4.7 m.Eq. in the second post-insulin hour. The test is negative by Hollander's criteria. A repeated test on 31.10.68 was unequivocally positive and the patient subsequently underwent re-vagotomy for recurrent ulcer.

Example 2. - W.H. (Truncal Vagotomy and Gastro-enterostomy
21/4/64)

I.S.T. 23.6.69

<u>Time</u>	<u>Volume</u> (mls.)	<u>Conc.</u> (m.Eq./l)	<u>Output</u> (m.Eq.)	<u>Blood Glucose</u> (mgms.%)
Basal	55	34	1.9	86
0-20'	5	47	0.2	
20-40'	5	30	0.15	
40-60'	7	45	0.3	36
60-80'	38	42	1.6	
80-100'	122	32	4.0	
100-200'	26	28	0.7	
			<hr/> 7.0 m.Eq./2 hrs. <hr/>	

Comment: The basal acid output of 1.9 m.Eq./hour, assuming adequate evacuation of fasting juice, is above the expected level (our mean basal acid output in 27 patients studied with unequivocally negative tests was $0.5 \pm$ S.D. 0.1 m.Eq./hr). The rise in volume giving a second hour output of 6.3 m.Eq. is grossly abnormal. Since there was no corresponding rise in concentration/

concentration the test is negative by Hollander's criteria. This patient is suspected, on clinical grounds, of having a recurrent ulcer.

Example 3. - I.S. (Truncal Vagotomy & Pyloroplasty 1/8/60)

I.S.T. 24/8/60

<u>Time</u>	<u>Volume</u> (mls.)	<u>Conc.</u> (m.Eq./l)	<u>Output</u> (m.Eq.)	<u>Blood Glucose</u> (mgms.%)
Basal	41	80	3.2	77
0-20	4	81	0.3	
20-40	6	96	0.5	
40-60	10	71	0.7	43
60-80	27	76	2.0	
80-100	28	88	3.3	
100-120	31	88	2.7	
			<hr/> 9.5 m.Eq./2 hrs. <hr/>	

Comment: Abnormally high concentration of basal juice.

A late volume response giving a total of 8.0 m.Eq. in the second hour. Negative by Hollander's criteria. No symptoms of recurrent ulcer. This test was probably performed too soon after operation.

These examples could be duplicated several times from our series. It is worthy of comment that these patients produced 4.7, 6.3 and 8.0 m.Eq. of acid in the peak hour after insulin. In the series under study there are 54 Hollander-positive tests. Of these no fewer than 15 (28%) show a peak hour output of less than 4.5 m.Eq. Furthermore 4 out of 25 patients with recurrent ulcer/

ulcer also showed a peak hour output of 4.5 m.Eq. or less.

Similar experience has led many workers to suggest alternative criteria and these have been summarised in the introduction to this section (Chapter 9) and are also presented in tabulated form below:-

Criteria for Interpretation of Insulin Test

1. A rise in acid concentration (above basal) of 20 m.Eq./l or of 10 m.Eq./l if basal secretion is anacid. Hollander (1948).
2. A rise in volume after insulin (Waddell 1957).
3. A basal acid output greater than 2 m.Eq./hr. (Bachrach 1962).
4. A rise in acid concentration (as in (1)) designated 'early' if within 45 minutes and 'late' if within 45 - 120 minutes (Ross and Kay 1964).
5. An increase of 1.5 m.Eq. in free or 2.0 m.Eq. in total acid in any hour after insulin (Bank, Marks and Louw 1967).
6. A rise in acid concentration (as in (1)) designated 'early' if within 60 minutes and 'late' if within 60 - 120 minutes (Johnson, Thomas, Checketts and Duthie 1967).

(Modified from Duthie 1969)

The/

The purpose of this study is to analyse our post-operative tests both by the criteria of Hollander and by multiple criteria in order to determine which should be used in our future clinical practice.

Materials and Methods

A series of 344 gastric surgical patients has been studied. Of these 170 underwent vagotomy, selective or truncal, combined with a drainage procedure. This group is chosen as suitable for analysis in respect of insulin testing. Exclusion of patients with vagotomy combined with resection is necessary because of the variable effect of antrectomy upon vagally mediated secretion (Chapters 7 and 8).

The techniques of insulin (I.S.T.) and maximal acid (M.A.O.) tests have been described previously (Chapter 12).

Results

The tests to be examined have been carried out at variable times after operation. One hundred and eighty five I.S.T.'s have been performed in 170 patients. Sixty five (36%) I.S.T.'s were performed before the patients left hospital, the remainder after periods varying between two months and fifteen years after operation. The majority 103 (54%) were carried out after discharge from hospital but within 5 years of operation. The following table summarises these time-relationships.

TABLE III, 12/

TABLE III, 12INSULIN TESTS: TIME AFTER OPERATION

Before leaving hospital	65 (36%)
$\frac{1}{2}$ - 1 year	59 (33%)
1 - 5 years	44 (25%)
5 - 10 years	8 (4%)
More than 10 years	4 (2%)

A feature of tests conducted within 2 - 3 weeks of operation, as anyone who has attempted them well knows, is that gastric stasis and excessive gastric mucus-production commonly make it very difficult to obtain satisfactory material for titration. Dilution of gastric contents by alkaline duodenal or jejunal juice, especially with the stomal dysfunction commonly seen in the early post-operative period after gastro-enterostomy, may also affect titrations.

It is necessary therefore to determine whether we can rely upon the early post-operative tests which constitute 36% of our series. Fifteen patients in this series underwent two or more tests at different times after operation. The results of these tests, as judged by conventional Hollander's criteria are listed below.

TABLE III, 13/

TABLE III, 13
REPEATED INSULIN TESTS

	<u>Early</u>	<u>0-1 yr.</u>	<u>1-5 yrs.</u>	<u>More than 5 yrs.</u>	<u>Results</u>
1.	-	+ve	-	+ve	Same
2.	-ve	+ve	-	-	Changed
3.	+ve	-	+ve	-	Same
4.	-ve	-	-ve	-	Same
5.	-ve	-ve	-	-	Same
6.	+ve	-	-ve	-	Changed
7.	-ve	-	-ve	-	Same
8.	+ve	-	-ve	-	Changed
9.	-ve	-	+ve	-	Changed
10.	-ve	-ve	-	-	Same
11.	-ve	-	+ve	-	Changed
12.	-ve	-	-	-ve	Same
13.	+ve	-	+ve	-	Same
14.	+ve	-ve	-	-	Changed
15.	-ve	-	+ve	-	Changed

It will be seen that no fewer than 7 out of 15 or 47% gave results in the early post-operative period which were reversed by later tests. Approximately equal numbers were false-positive as false-negative. While larger numbers and repetition of tests at both phases were obviously desirable it must be concluded on this evidence that early post-operative tests do not provide a reliable guide to long term assessment. This is an area that clearly merits further study, and one to which scant attention has been paid in the literature.

Further/

Further analysis of post-operative tests therefore excludes those carried out in the early post-operative period. Five tests have also been discarded as technically faulty (inconsistent volume sampling or gross contamination by retained or refluxed material). We are thus left with 110 post-operative insulin tests. Of these 110, 45 patients also underwent tests of maximal acid output (M.A.O.) at approximately the same time. The relationships between insulin-stimulated acid output and both maximal acid output and basal secretion are outlined in the following chapters.

CHAPTER 14

INTERPRETATION OF THE INSULIN TEST

II. VAGOTOMY AND THE MAXIMAL ACID OUTPUT

It is widely accepted that vagotomy reduces the maximal acid response (M.A.O.) to histamine or pentagastrin by approximately 70% (Gillespie 1960, Kyle 1951, Payne and Kay, 1962). It is re-emphasised that the term 'maximal' acid output, as used in this thesis, refers to the responses obtained to 0.04 mgms./kg. histamine or 6.0 ug./kg. pentagastrin by the subcutaneous route. It is acknowledged that these do not represent the highest responses of which the stomach is capable when these stimulants are given for example by the intravenous route.

Although it is agreed that patients with recurrent ulcer tend to have a higher M.A.O. than those with negative insulin tests a sufficiently consistent pattern has not been found for the M.A.O. to be advocated as a test for completeness of vagotomy (Duthie 1969).

Materials and Methods

After exclusion of patients who had undergone vagotomy combined with resection and elimination of tests performed within two to three weeks of operation there were 70 patients in/

in this series who had had tests of both maximal and insulin-stimulated acid output after vagotomy.

The methods of performing the tests and the definition of 'maximal' acid output (M.A.O.) have been outlined earlier (Chapter 12). Where patients underwent more than one M.A.O. the highest results obtained have been selected. Pre-operative studies in 314 patients (Chapter 12) showed a mean M.A.O. of $40.3 \pm$ S.D. 7.3 m.Eq./hr. and a mean concentration of $125.3 \pm$ S.D. 17.2 m.Eq./l.

It is the purpose of this chapter to analyse the effects of vagotomy upon the M.A.O. and to determine whether these effects can be correlated with the insulin response as judged by multiple criteria.

Results

The findings are summarised in Table III, 14 and represented diagrammatically in Fig. III, 15. It will be seen that there is a close correlation between the mean M.A.O. and the degree of 'positivity' of the post-insulin response. But, as the ranges show, the correlation is not a uniform one. It is perhaps worth noting that three quarters of the patients diagnosed as having recurrent ulcer had M.A.O.'s of greater than 10 m.Eq. per hour.

An alternative approach is to consider the extent to which the/

INSULIN-STIMULATED ACID OUTPUT AND THE MAXIMAL ACID OUTPUT

Result of I.S.T. (multiple criteria)	No. of Cases	Maximal Acid Output	
		Mean & S.D.	Range
Negative	26	1.9 \pm 0.3	0.0- 5.8
+	13	3.4 \pm 0.6	0.3- 7.0
++	3	8.5 \pm 1.9	5.2- 8.3
+++	11	8.8 \pm 2.1	1.5-24.0
++++	8	16.9 \pm 3.3	6.8-30.0
+++++	9	22.1 \pm 4.6	6.9-47.0
Recurrent Ulcer*	19	19.3 \pm 2.4	7.6-33.0
**Recurrent Ulcer* includes both proven cases and patients suspected of having recurrent ulcer on grounds of abdominal pain or haemorrhage.			

TABLE III, 14

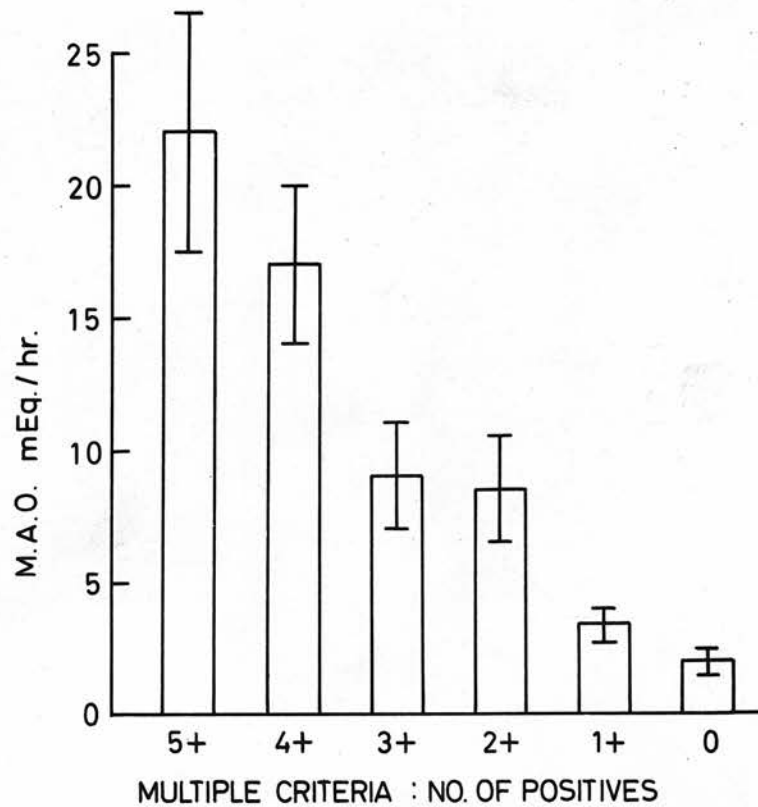


Fig III, 15. The post-operative response to maximal histamine or peptavlon stimulation. 71 patients have been divided according to the type of insulin-stimulated response as judged by multiple criteria. Each column represents a mean with one standard deviation.

the M.A.O. has been reduced by the vagotomy. The results are shown in Table III, 16, the reduction being expressed as percentage of pre-operative M.A.O. Again a clear general trend for the strongly positive insulin response to be associated with a smaller reduction in M.A.O. is visible. The ranges however are so wide that, in considering the individual patient, the measurements may be unhelpful. The values obtained in the insulin-negative and the one-plus positive patients (range 0-29%) firmly support the view that complete vagotomy reduces the M.A.O. by 70% or more (Payne and Kay 1962).

If one is to invoke multiple criteria in interpreting the insulin test one wishes to know how many criteria should be positive to achieve significance. As a possible means of indicating this the differences between M.A.O.'s, and also in the percentage reduction in M.A.O., have been tested by the Student *t* test. The post-insulin responses have been divided according to the number of criteria which are positive (zero to 5+) as illustrated in Tables III, 14 and 16. The data from the recurrent ulcer group are included for comparison. The secretory characteristics of this group will be discussed in Chapter 17.

M.A.O. Peak Concentration

The difference between zero and 1- positive was significant at the 5% level. The two-positive group contained insufficient data./

INSULIN-STIMULATED ACID OUTPUT AND THE PERCENTAGE TO WHICH VAGOTOMY
REDUCES THE MAXIMAL ACID OUTPUT

Result of I.S.T. (multiple criteria)	No. of Cases	M.A.O. as % of Pre-op. M.A.O.	
		Mean \pm S.D.	Range
Negative	24	7.8 \pm 1.7	0- 29
+	11	7.0 \pm 1.7	1- 18
++	insufficient	-	-
+++	10	25.0 \pm 7.0	5- 77
++++	7	44.7 \pm 10.8	11-100
+++++	8	57.0 \pm 8.0	22- 93
Recurrent Ulcer*	14	55.2 \pm 8.0	11-100
<p>*This group includes patients with proven recurrent ulcer and also patients suspected of having recurrence on grounds of abdominal pain or haemorrhage.</p>			

TABLE III, 16

data. The difference between the zero and 3-positive group was highly significant ($p = 0.001$).

Testing the combined 1 and 2-positives versus the 3-positives the difference was significant ($0.02 < p < 0.05$). There was no statistical difference between 3-positive and 4-positive, nor between 4-positive and 5-positive.

Grouping the data 1 + 2 + 3-positive versus 4 + 5-positive showed a highly significant difference. Testing 1 + 2-positive versus 3 + 4 + 5-positive also showed a highly significant difference. The 't' value was higher in the latter grouping but in both cases the significance was at the 0.1% level ($p = 0.001$).

M.A.O.

The same comparisons were made for the M.A.O. (m.Eq./hour). The difference between the mean M.A.O. in the zero and 1-positive groups was only significant at the 5% level, but between zero and 2-positive this reached the 0.1% level ($p = 0.001$). Comparing adjacent groups, only the difference between 3-positive and 4-positive achieved significance ($0.01 < p < 0.02$).

Combining the groups gave the highest 't' value when testing 1 + 2 + 3-positive against 4 + 5-positive ($p = 0.001$) although a similar level of significance still showed if 3-positive was aligned with 4 and 5.

Reduction/

Reduction in M.A.O.

Statistical comparisons of the mean percentages to which the M.A.O. was reduced by vagotomy gave exactly the same findings as when the absolute M.A.O. was considered.

Conclusion

After vagotomy close correlations can be demonstrated between the maximally-stimulated acid concentration, the acid output and the percentage to which the M.A.O. is reduced on the one hand and the number of positive criteria on the other. The greatest level of statistical difference appeared to lie between the 3 and 4-positive levels.

CHAPTER 15INTERPRETATION OF THE INSULIN TESTIII VAGOTOMY AND THE BASAL ACID OUTPUT

The 'basal' or 'spontaneous' acid is that produced by the empty, resting, unstimulated stomach. There is general agreement that it provides an indication of parasympathetic activity or 'vagal-tone'. An elevated basal output in the post-vagotomy patients, in the absence of any abnormal stimulus such as that provided by a Zollinger-Ellison type of tumour, may therefore be the first indication of incomplete vagotomy. Bachrach (1962) advised that a basal secretion of 2 m.Eq. per hour or more was evidence of incomplete vagotomy. Hollander (1946) used the basal concentration as his most significant base-line.

Studies on patients before operation (Chapter 12) showed the mean basal output in 314 patients was $5.2 \pm$ S.D. 0.3 m.Eq./hr. The mean basal concentration in the un-vagotomised stomach was $49.2 \pm$ S.D. 1.5 m.Eq./l.

The purpose of this chapter is to describe the effects of vagotomy upon basal secretion and to relate these effects to the analysis of the post-insulin response by multiple criteria.

Materials/

Materials and Methods

Our methods of conducting gastric secretion tests have been outlined in Chapter 12. Although a few patients in this series underwent 12-hour overnight tests of basal secretion or 3-hour basal collections the majority of the data are derived from basal collections made during the hour preceding histamine, pentagastrin or insulin stimulation. Most patients underwent several tests and therefore the mean basal output was calculated. Suitable measurements of basal juice were available in 85 patients who also had insulin tests. Early post-operative tests and tests in patients who had had gastric resection were excluded.

The basal concentrations and 1-hour outputs are related to the post-insulin response.

Results

Table III, 17 shows a tendency for the basal concentration to rise the more positive criteria were present. There is however no statistically significant difference between the means of successive groups beyond the 2-positive level. The only significant increments were between zero and 1-positive ($0.02 < p < 0.05$) and between 1 and 2-positive levels ($0.001 < p < 0.002$).

Correlations between basal output and post-insulin response are/

THE BASAL ACID CONCENTRATION AND THE POST-INSULIN
RESPONSE: MULTIPLE CRITERIA

Insulin Response (Multiple Criteria)	No. of Cases	Mean Conc.: & S.D. (m.Eq/l)	Range
Negative	31	10.2 \pm 1.4	0- 24
+	16	16.0 \pm 2.4	0- 29
++	6	40.3 \pm 8.5	26- 82
+++	12	31.2 \pm 6.0	9- 73
++++	10	41.1 \pm 7.6	12- 85
+++++	10	41.6 \pm 3.6	14-111
Recurrent Ulcer*	22	41.5 \pm 3.1	14-111
*This group includes patients with proven recurrent ulcer and also patients suspected of having recurrence on grounds of abdominal pain or haemorrhage.			

TABLE III, 17

THE BASAL ACID OUTPUT AND THE POST-INSULIN RESPONSE:
MULTIPLE CRITERIA

Insulin Response (Multiple Criteria)	No. of Cases	Mean Output & S.D. (mEq/hr)	Range
Negative	31	0.5 ± 0.1	0-1.5
+	16	0.8 ± 0.3	0-3.8
++	6	1.3 ± 0.3	0.7-2.2
+++	12	2.2 ± 0.4	0.6-4.2
++++	10	3.6 ± 0.8	0.4-8.6
+++++	10	3.6 ± 0.7	1.2-6.7
Recurrent Ulcer	22	3.1 ± 0.4	0.1-6.9

TABLE III, 18

are shown in Table III, 18. No significant difference existed between the increment between any adjacent group from 0 - 5-positive. When combined groups of positives were tested a highly significant difference ($p = 0.001$) could be shown between 1 + 2 and 4 + 5-positive. Adding the 3-positive group to either side did not alter the degree of significance.

In Tables III, 17 and 18 the data for recurrent ulcer are also shown for comparison.

Summary

There is a rise both in basal concentration and total acid output in proportion to the number of positive criteria. This correlation holds only as far as the 2-positive level in respect of concentration and the 3-positive level in respect of output. The ranges of basal acid in all groups were such that in the individual case assessment of completeness of vagotomy upon this criterion alone can be of little value. Discussion of this material is deferred to Chapter 17.

CHAPTER 16INTERPRETATION OF THE INSULIN TESTIV THE TIMING OF THE POSITIVE RESPONSE

In analysing a series of 100 post-operative insulin tests Ross and Kay (1964) noted that of the 38 patients who showed a positive response by Hollander's criteria 9 showed a response within 45 minutes of insulin administration while the remaining 29 gave a response between 45 and 120 minutes later. These tests were conducted between the 7th and 10th days after operation. In 7 patients the test was repeated after 'several months' and the response remained 'true to type'. The authors were able to exclude differences in age, weight, level of hypoglycaemia and augmented histamine responses as causative factors.

Two important observations were made by these authors. Firstly they noted that the 'early-positive' response correlated with the smallest reduction in the augmented histamine response (9.4%) while patients with 'late-positive' responses had mean reductions of 53.2% and those with negative insulin tests had mean reduction of 67.4%, and secondly that patients with recurrent ulcer were all within the early-positive group. Kay and his colleagues have continued to use the early positive response therefore as their criterion of incomplete vagotomy (Gillespie, /

(Gillespie, Gillespie and Kay 1968). They have attributed the differences in timing of the post-insulin response to corresponding differences in size of the vagal fibres left by the surgeon and they have regarded the small residual fibres responsible for the late response as probably not significant in ulcer recurrence. The evidence that the vagus can regenerate both by bridging a gap or by innervation of distal axon sheaths by lateral sprouting (Murray 1965) suggests that this assumption may not be correct.

Griffiths and colleagues have provided support for the anatomical explanation for the early and late positive responses with an interesting series of animal experiments. Firstly they demonstrated that electrical stimulation of dissected vagal branches in the dog could provoke acid secretion from defined areas of the gastric mucosa proportional in size to the size and location of the nerve stimulated (Pritchard, Griffiths and Harkins 1968). Secondly they showed by secretion studies in the pylorus-ligated rat that acid output and ulcerogenesis could be correlated with the size of the intact nerve. A third finding was that they could demonstrate similar results by insulin-stimulation of selectively preserved fibres in the dog and, particularly german to the present discussion, that they could demonstrate a delayed response if they left intact

a/

a nerve which supplied the antrum, thus invoking the neuro-hormonal pathway (Legros and Griffiths 1968). This latter finding was at variance with Ross and Kay (1964) who, in the human, still demonstrated the late-positive response in patients after antrectomy.

As an alternative to the 'early' response within 45 minutes and the 'late' response from 45 to 120 minutes Johnston, Thomas, Checketts and Duthie (1967) have suggested division of the post-insulin responses into an 'early' response occurring within the first hour and a 'late' response in the second hour. A positive response is still defined by the criteria of Hollander, namely a rise of 20 m.Eq./l above the basal concentration (or 10 m.Eq./l if the basal juice is anacid).

In this chapter the results of our insulin tests are analysed according to the correlation of first and second hour post-insulin responses with other criteria of incomplete vagotomy.

Materials and Methods

The methods of conducting gastric secretion tests in this series have already been outlined (Chapter 12).

Of 344 patients available for study 170 underwent vagotomy combined with a drainage procedure. Patients who had antrectomy are excluded from this analysis. Early post-operative tests have been included in this analysis since at this point we are considering/

considering purely positive tests. Available for study are 59 Hollander-positive tests. Forty five (66%) occurred within the first hour, the remaining 15 (33%) in the second.

No difference in age, sex or pre-operative M.A.O. is apparent between these two groups.

The two groups are compared firstly for any differences between the insulin stimulated responses themselves and secondly for correlations with changes in M.A.O. or basal secretion.

Comparison of Post-Insulin Responses

The results of comparing the early and late positive responses to insulin hypoglycaemia are shown in Table III, 19; the range of volumes was very wide and there was no significant difference between the means.

The differences between mean peak concentration and mean peak one-hour outputs in the two groups was significant at the 5% level when tested by the Student 't' test.

Comparison of Maximal Acid Outputs

Fifteen patients in the 'early' group had M.A.O. tests also performed (Table III, 20). The mean output was 16.9 ± 2.9 m.Eq./hr. Only 7 patients had M.A.O.'s in the late group; the mean was $9.1 \pm$ S.D. 2.1 m.Eq./hr. and this difference was not statistically significant by the Student 't' test. Similarly although there was a difference in mean peak concentrations - $97.6 \pm$ S.D. 7.8 m.Eq./l and $68.1 \pm$ S.D. 16.6 - this did not reach significant/

COMPARISON OF THE EARLY
AND LATE POSITIVE RESPONSES
TO INSULIN STIMULATION

Timing of Response	Volume (mls)		Conc. (m.Eq/l)		1-Hour Output (m.Eq)	
	Mean \pm S.D.	Range	Mean \pm S.D.	Range	Mean \pm S.D.	Range
<u>Early</u> (45 Patients)	142 \pm 101	25 - 330	88 \pm 25	40 - 140	10.6 \pm 8.9	0.5 - 48.0
<u>Late</u> (15 Patients)	108 \pm 72	54 - 320	68 \pm 26	36 - 126	5.7 \pm 3.1	2.0 - 12.1
<u>Significance</u>	N.S.	-	p = < 0.05	-	p = 0.05	-

TABLE III, 19

THE MAXIMAL ACID OUTPUT AND THE
TIMING OF THE INSULIN-STIMULATED
POSITIVE RESPONSE

	Early-Positive (15 patients)		Late-Positive (7 patients)		Significance
	Mean & S.D.	Range	Mean & S.D.	Range	
1-Hr. M.A.O. (m.Eq)	16.9 \pm 2.9	1.5 - 33.0	9.1 \pm 2.4	0.5 - 9.0	N.S.
M.A.O. Conc: (m.Eq/l)	97.6 \pm 7.8	35 - 147	68.1 \pm 16.6	10 - 123	N.S.
M.A.O. % of pre-op:	45 \pm 7	11 - 93	13 \pm 7	5 - 30	p > 0.05

TABLE III, 20

significant levels. However the percentage reduction in M.A.O. ($45 \pm$ S.D. 7% and $13 \pm$ S.D. 7% respectively) did reach statistical significance ($0.02 < p < 0.05$).

Comparison of Basal Acid Outputs

The means of the basal acid outputs and concentrations are shown in Table III, 21. The differences between the early and late positive groups were not statistically significant.

Recurrent Ulcer and the Timing of the Insulin-Stimulated Response

The question of the gastric secretory characteristics of patients with recurrent ulcer is discussed more fully in the next chapter. Patients with positive insulin tests were divided into those with no symptoms of recurrent ulcer (35) and those who had recurrent ulcer proven or suspected on clinical grounds of recurrence of typical pain or upper gastrointestinal haemorrhage (25). In the 'no ulcer' group 11 (31%) showed late positive responses, while in the 'recurrent ulcer' group 4 (16%) gave late-positive responses. Testing these differences by Chi square shows them not to be significantly different.

Summary

In this study the strength of the post-insulin response, as measured by acid concentration and peak one hour acid output was significantly greater in the early-positive group.

Apparent/

Apparent differences in maximal acid output, basal acid output and incidence of recurrent ulceration failed to reach statistically significant levels. Significantly greater reduction of the maximal acid output was noted in the early-positive group. Discussion of the clinical significance of these findings is deferred to the following chapter.

BASAL ACID AND THE TIMING OF THE POSITIVE RESPONSE

	Early Positive (cases)		Late Positive (cases)		Significance
	Mean \pm S.D.	Range	Mean \pm S.D.	Range	
Basal Output (m.Eq/hr.)	2.9 \pm 0.5	0.4 - 6.9	2.2 \pm 0.7	0 - 8.6	p>0.05
Basal Conc.: (m.Eq/l)	37 \pm 6	9 - 111	31 \pm 5	0 - 78	p>0.05

TABLE III, 21

CHAPTER 17INTERPRETATION OF THE INSULIN TESTV: RECURRENT ULCER

It has been claimed that peptic ulcer can recur in the presence of complete vagotomy (Clark, Murray Slessor and Wyllie, 1964; Bryant, Klein and Griffen 1966; Nobles 1966). This is of course true in the case of the Zollinger-Ellison syndrome. In the absence of any such abnormal source of polypeptide gastric stimulant, and excluding the special situation of suture-line ulcer due to the presence of non-absorbable suture material at the anastomosis, the evidence that recurrent ulcer may follow complete vagotomy must be regarded with suspicion.=

The first two groups quoted above reported a total of eight cases of recurrent ulcer in the presence of complete vagotomy. Neither group give any evidence of having carried out repeated tests to confirm their findings nor did they give details of their method of insulin testing, beyond referring to the work of Hollander (1946). It may be assumed therefore that insulin doses of 15 - 20 u/kg. were used. The third author (Nobles 1966) claimed an incidence of 26% of insulin-fast achlorhydria in patients with recurrent ulcer. It should be pointed out however that he conducted his post-operative tests one month after operation. Our data suggest that this may be too early for/

for reliable results. Furthermore his description of the insulin test gives no grounds for confidence in the data. After 20 units of insulin "the titratable gastric acidity was measured for one or two hours".

Such are the individual variations in sensitivity to insulin, the marked inhibitory effects of insulin in the doses used by these workers and the profound depression of secretion demonstrated in patients with unequivocally negative insulin responses observed in this and other series that further evidence is required before the association of complete vagotomy with recurrent ulcer can be accepted. Such evidence could take the form of secretion tests using 2-deoxy-D-glucose or minimal doses of insulin and histological examination of tissues obtained after thorough search of the abdominal oesophagus.

Should the case for recurrent ulcer in the presence of complete vagotomy be substantiated it would confirm the hypothesis that patients differ in the relative importance of the neural and hormonal paths of gastric stimulation. Attempts to differentiate such patients by blocking the vagus pharmacologically with hexamethonium bromide 25 mgms. and atropine 0.3 mgms. (medical vagotomy) (Gillespie and Kay 1961) or by propantheline bromide (Checketts, Gillespie and Kay 1966), although showing good correlation between the mean results of surgical and medical/

medical vagotomy appear to be of doubtful value in the individual case (Johnston, Goligher and Duthie 1966).

To summarise the foregoing discussion a current view of the position is provided by Kay (1969):-

"The incidence of recurrent ulceration after vagotomy compares unfavourably with that after partial gastrectomy and is probably not less than 5 per cent. Although there is some evidence that division of all vagal branches to the stomach does not confer immunity to this complication it is generally agreed that incomplete nerve section is the commonest cause".

A more emphatic view, which I believe to be the correct one, is advanced by Stempien, Lee and Dagradi (1968) in a well-documented series of 150 insulin tests drawn from a series from over 625:-

"... in our experience over a span of 20 years, an adequate vagotomy as measured by a reliable insulin test has never been associated with recurrence of peptic ulcer disease - duodenal, gastric or stomal. We believe any reports to the contrary to be based on inadequate test procedure, mistaken interpretation of test results, or because of the inducement of peptic ulcer through an extravagal/

extravagal pathogenesis - as in the Zollinger-Ellison syndrome".

The incidence of incomplete vagotomy in the medical literature ranges between 10 and 40%, (Kay 1969). It is clear that not all patients with incomplete vagotomy develop recurrent ulceration. Having analysed the insulin secretion test in some depth in the previous chapters the most valuable information which could be extracted would be a demonstration of the secretory characteristics of patients likely to develop recurrent ulcer.

It is the purpose of this chapter to analyse the secretion tests upon patients with and without recurrent ulcer and to establish which criteria are the most informative in detecting the patient 'at risk'.

Materials and Methods

The techniques of the secretion tests and the factors governing selection of reliable tests have been described in previous chapters. Available for analysis are Hollander-positive post-operative insulin tests performed on 59 patients. This represents the same group analysed in respect of timing of response in the previous chapter. The positive criteria used in this study are Nos. 1, 2, 3, 4 and 6 listed on p. 152, Chapter 13.

It/

It has proved difficult to decide what constitutes a recurrent ulcer. Radiology and endoscopy are well-recognised to have a high rate of failure in this context. Even at operation it may be difficult (and undesirable) to demonstrate an ulcer crater with certainty. In addition to those proven at operation therefore one third of the 'recurrent ulcer' group in this study includes patients who were investigated on suspicion of having recurrence on grounds either of return of ulcer type of pain or of upper gastro-intestinal haemorrhage.

Results

Using an approach similar to that described in previous chapters in assessing the several available secretory indices these two groups have been compared in respect of the M.A.O., basal and insulin-stimulated secretions.

The M.A.O. and Recurrent Ulcer

In the 'no-recurrence' group 16 out of 35 patients and in the 'recurrent' group 19 out of 25 had M.A.O.'s in addition to I.S.T.'s. This difference is due, as one would expect, to the extra investigations performed in the latter group. The results are shown in Table III, 22. It is evident that there was no significant difference in concentration of acid produced by the two groups. The difference between volumes was significant/

THE MAXIMAL ACID OUTPUT AND RECURRENT ULCER

	Volume (mls.)		Peak Conc: (m.Eq/l)		1-Hr. Output (m.Eq)	
	Mean \pm S.D.	Range	Mean \pm S.D.	Range	Mean \pm S.D.	Range
Recurrence (19 Patients)	214 \pm 26	80 - 455	104 \pm 11	62 - 140	19.3 \pm 2.4	6.8 - 33.0
No Recurrence (16 Patients)	157 \pm 19	39 - 304	87 \pm 10	10 - 145	10.6 \pm 1.6	1.0 - 20.0
Significance (By Student t)	0.01 $< p < 0.05$	-	N.S.	-	0.002 $< p < 0.01$	-

TABLE III, 22

BASAL ACID OUTPUT AND RECURRENT ULCER

	Conc: (m.Eq/l)		1-Hr. Output (m.Eq)	
	Mean \pm S.D.	Range	Mean \pm S.D.	Range
Recurrence (22 patients)	42 \pm 4.8	14 - 111	3.1 \pm 0.4	0.1 - 6.9
No recurrence (33 patients)	28 \pm 3	0 - 70	1.8 \pm 0.2	0 - 4.6
Significance	0.01 < p < 0.02	-	0.002 < p < 0.01	-

TABLE III, 23

significant at the 5% level and the difference in acid output was highly significant when analysed by the Student 't' test ($0.01 < p < 0.02$).

The post-operative M.A.O. was calculated as per cent of the pre-operative M.A.O. for each case. The means were $55 \pm$ S.D. 8% in the 'recurrent' group and $27 \pm$ S.D. 4.1 in the 'No-recurrence' group. This difference was highly significant ($0.002 < p < 0.01$).

The Basal Acid and Recurrent Ulcer

Data of basal acid secretion were available in 22 of the 'recurrent' group and 33 of the 'no-recurrence' group. The results are summarised in Table III, 23. The difference in mean concentration was significant ($0.01 < p < 0.02$) as was also the difference in 1-hour output ($0.002 < p < 0.01$).

Recurrent Ulcer and Multiple Criteria

If the 59 Hollander-positive patients are grouped according to the number of positive criteria the distribution of recurrent ulcer patients within these groups is fairly striking.

TABLE III, 24

THE NUMBER OF POSITIVE CRITERIA IN RECURRENT ULCER

Number of +ve criteria	3 +ve	4 +ve	5 +ve
Number of Patients	20	26	13
Recurrent Ulcer	2(10%)	12(46%)	10(77%)

These/

These data are presented in histogram form in Fig. III, 25. One patient with recurrent ulcer, whose insulin response showed only 2 positive criteria, is not included.

Recurrent Ulcer and the Timing of the Response

Division of the same patients into 'early' and 'late' positive responses and their relationship to recurrent ulcer is shown below.

TABLE III, 26

Timing of Response	Early Positive	Late Positive
Number of Patients	44	15
Recurrent Ulcer	21 (48%)	4 (27%)

These data are represented by histogram in Fig. III, 27. The association of recurrent ulcer with the 'early' positive response is less striking than with the 5-positive response. The presence of a 'late' positive response does not preclude recurrent ulceration.

If the patients with 4 or 5-positive criteria (39 patients) are taken as a group, and to these are added only the patients in the 3-positive group who had an early response (5 patients) we have a group of 44 patients of whom 22 (50%) had recurrent ulcer./

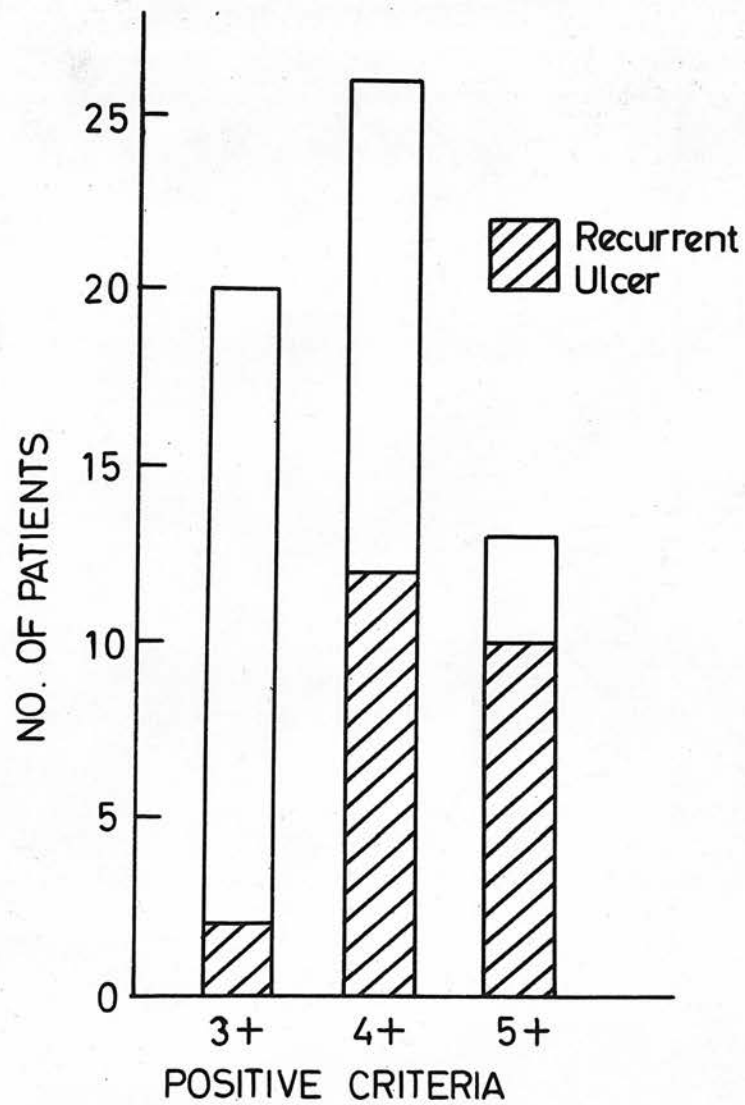


Fig III, 25. Recurrent ulcer in patients with 3 or more positive criteria after insulin stimulation.

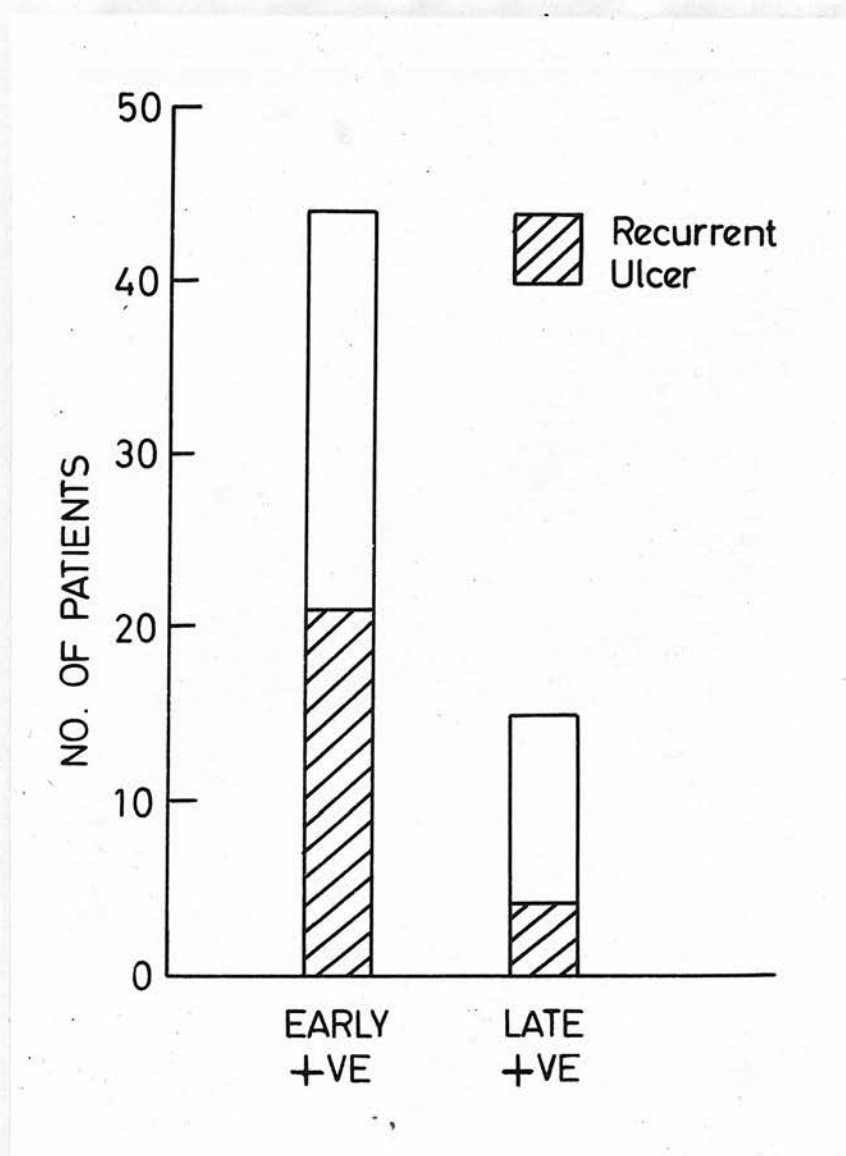


Fig III, 27. Recurrent ulcer and the timing of the positive response to insulin in 60 patients.

ulcer. By this process of selection in fact only 2 recurrent ulcer patients are missed! They had a 2-positive late response and a 3-positive late response respectively. Expressed differently it appears that 22 out of 24 patients (91%) with recurrent ulcer had insulin tests showing either a 3-positive response which included an early positive rise or a 4-positive response which might include an 'early' or a 'late' positive or a 5-positive response (which, by definition, includes an 'early' positive rise).

Finally, in Fig. III, 28, the various types of positive response have been compared in histogram form, along with their corresponding mean maximal and basal acid outputs, thus summarising in effect the subject matter of chapters 14 - 17. The groups are not mutually exclusive. For example the left hand group (R - U) contains all the patients defined earlier as having recurrent ulcer. These patients are distributed, in diminishing proportions as indicated in Tables III, 24 and III, 26 throughout the other groups with the exception of the 'H+ve' group which represents all those without recurrent ulcer but with tests positive by Hollander's criteria. The incidence of recurrent ulcer in each of these groups is shown in Fig. III, 29.

Discussion/

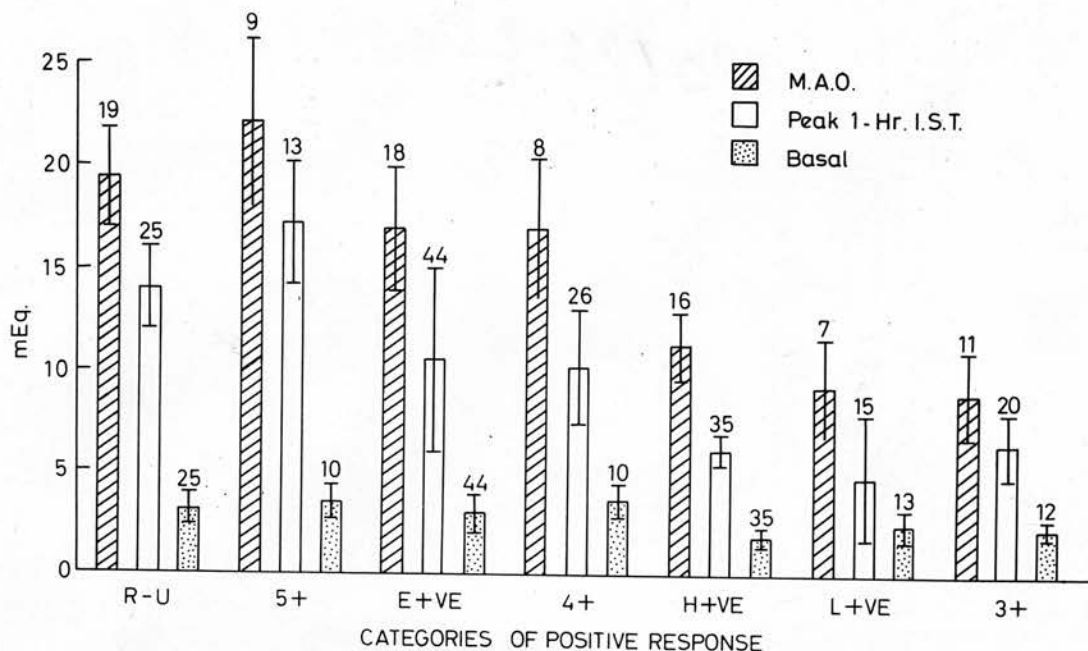


Fig III, 28. The M.A.O., peak 1-hour insulin and basal outputs grouped according to categories of positive response.

Each column represents a mean. The number of patients in each group and one standard deviation above and below the mean are shown at top of each column. Multiple criteria from 3 to 5-positive are included. 'E +ve' = first hour response; 'L +ve' = 2nd hour; 'R-U' = recurrent ulcer; 'H +ve' = Hollander-positive but excluding patients with recurrent ulcer. The groups are not mutually exclusive; for example a patient with an early-positive rise will also appear in the 4 or 5-positive group.

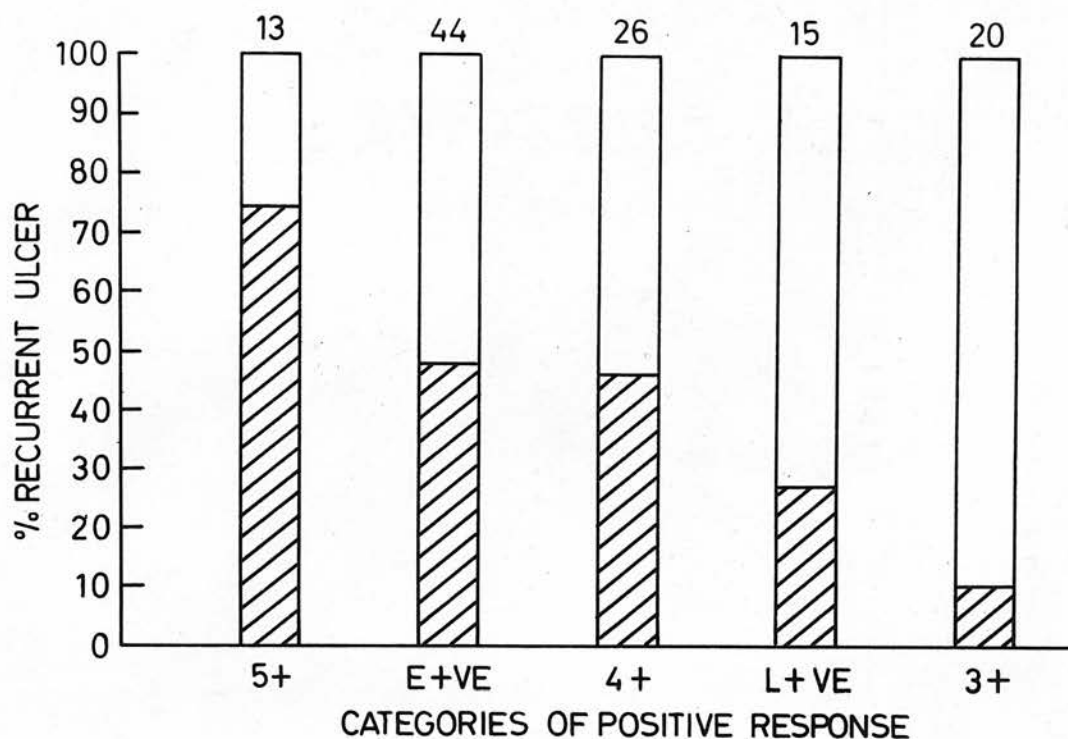


Fig III, 29. Categories of positive response to insulin
in 60 patients.

The number of patients in each group is recorded above the appropriate column. The cross-hatched area represents the proportion of patients with recurrent ulcer.

Discussion

It would be gratifying if one could produce a formula which would forecast with certainty, on the basis of simple secretion tests, whether a patient was fated to develop recurrent ulcer. Predictably such a formula does not emerge from these studies although trends have appeared which should be of clinical value and should guide further inquiry.

Sources of Error

Certain areas of fallibility in this study must be recognised before interpretation of the data is attempted. Perhaps the most important is the question of time. Time may be critical in two aspects of the study. Firstly the patients tested had their operations at times varying from 15 years to six months ago, - the majority within the past 5 years. The duration of follow-up is discussed more fully in Chapter 20.

It is quite clear therefore that the full harvest of recurrent ulcers has yet to be reached. Small (1964) has reviewed the English medical literature upon the question of the time interval between operation and recurrence, as well as providing data derived from an experience of 83 patients with recurrent ulcer seen between 1947 and 1963 in this Unit. He concludes that there is no reason why the interval between gastro-enterostomy and vagotomy and recurrence should differ from

/the

the interval after gastro-enterostomy alone, namely an average of 16.4 years, with a range of 8 months to 38 years (Smithwick, Farmer and Harrower, 1963). Although our policy of selecting for vagotomy and drainage patients with higher maximal acid outputs than those selected for gastro-enterostomy alone (Bruce, Card, Marks and Sircus, 1959) might tend to promote earlier recurrence when vagotomy fails in the former group it must still be assumed that a number of patients will move from the insulin-positive 'no-recurrence' to the insulin-positive 'recurrence' group during the next decade and beyond. For this reason it is hoped that this data will accumulate and continue to be kept under periodic review.

The second time factor which must be acknowledged is that of the interval between operation and gastric testing. Information upon the long-term behaviour of secretory function as demonstrated by repeated tests is scanty. Our initial results (Chapter 13, page 155) appear to show insulin tests within 2-3 weeks of operation to be unreliable. Bell (1964) has reported on augmented histamine tests in 43 patients finding no difference between the responses 10 days and 1-3 years after vagotomy and drainage. This is at variance with the findings of Jepson and Johnston (1968) who performed tests immediately following and 9 months after vagotomy and drainage. They selected insulin-

/negative

negative patients for study and found a statistically significant fall in acid response to histalog and pentagastrin over the 9 month period. Perhaps the best material is provided by Bank, Marks and Louw (1966) who performed augmented histamine tests at first monthly and then yearly for four years upon 75 patients. They noted certain interesting facts. Some patients showed basal hypersecretion approximating the maximal acid output for a few weeks or months. Most of these patients had gastro-enterostomy with selective or truncal vagotomy. After an initial 70% decrease the MAO remained constant in the majority but showed a progressive decline in others, 11% becoming achlorhydric after vagotomy and drainage. These authors do not however report upon the long-term status of the insulin test.

A further preliminary point which must be made is that it is not certain that because particular secretory characteristics are demonstrated in patients with recurrent ulcer it necessarily follows that these characteristics can be translated to the 'no recurrence' group and used to forecast future trouble. Quite apart from the ill-understood complexities of individual variations in susceptibility to ulcer the presence of ulcer-induced acute or chronic inflammation at a stoma may promote changes in secretion which could not have been demonstrated before the ulcer began. For example interference with gastric emptying may augment the maximal secretory response (Sircus 1965).

/Broad

Broad conclusions are drawn from this series. More detailed deductions may become possible as further material, obtained by improved techniques becomes available.

Interpretation of the Insulin Test

Review of the material available from secretion studies in 344 patients (Chapter 13) has suggested that ruthless elimination of doubtful material is necessary when attempting analysis of a test as controversial as the insulin test. Analysis has therefore been confined for most purposes to late post-operative tests upon patients who had vagotomy with drainage. Some aspects of secretion tests after vagotomy with antrectomy are discussed in Chapter 6, page 67 and Chapter 8, page 97.

Changes in maximal and basal acid output were already well known to follow vagotomy. The principle followed in these analyses has been to study the increments in these two parameters - both in concentration and output (and thus indirectly also volume) to see where the biggest differences lay relative to increments in positive responses as judged by the multiple criteria, the criteria of Hollander (1946) Ross and Kay (1964) and Johnston, Thomas, Checketts and Duthie (1947) and finally by the ultimate criterion - recurrent ulcer.

A histogram summarising the findings in respect of acid output is shown in Fig. III, 28.

/Basal

Basal Acid

It has already been pointed out that basal acid collections, as performed under routine ward conditions appeared to be prone to technical error.

Although a significant difference was demonstrated between mean basal output in the recurrent ulcer group and the 'no-recurrence' group no significant increment could be found by relating basal acid to multiple criteria (Table III, 17). By pooling the groups the major difference was shown to occur between the 2 and 4 positive groups. In terms of concentration the only significant differences occurred between the 0 and 1 and between the 1 and 2 positive groups.

To some extent this is a difference which is artificially created by the construction of the positive groups. Criteria most commonly found positive were, in order of frequency, a rise in volume, a rise in basal output, a rise of more than 2mEq. in any one hour, a Hollander positive rise in concentration and finally an early-positive Hollander response. It follows therefore that a difference in basal output related to recurrent ulcer and a difference related to the timing of a Hollander response or any other criterion not directly related to the basal acid were more significant than differences among the lower ranks of the multiple criteria.

Furthermore in the ranges of basal acid concentration (Table III, 17) and output (Table III, 18) there is considerable overlap throughout the range from insulin negative to 5-positive

/which

which greatly diminishes its value as a single criterion.

Perhaps the best way to express the findings is that only 6 out of 22 (27%) patients with recurrent ulcer showed a basal acid below 2mEq. compared with 19 out of 33 (58%) in the 'no-recurrence' groups. Chi square analysis does not show this difference to be significant with the numbers presently available.

The Maximal Acid Output

Because they demonstrated significant differences between the amounts by which the augmented histamine response was reduced in the insulin negative, late positive and early positive groups, Ross and Kay (1964) suggested its use in the assessment of vagotomy. It was subsequently pointed out by Grossman (1964) that although the mean values of augmented histamine response in the three groups differed significantly there was an overlap between the early and late group amounting to 26%. He concluded that the response to insulin-stimulation was a more sensitive guide.

The same conclusion has been reached in this study (Chapter 14). A correlation was noted between rises in MAO and increments in positive response as judged by multiple criteria. The most striking transition occurring at the 3 positive level.

Differences in MAO when divided into early and late insulin positive groups were not significant, but when divided in this way the reduction in MAO was significant at the 5% level.

/Differences

Differences in MAO when divided into 'recurrent' and 'no-recurrent' ulcer groups were highly significant as were also differences in concentration and in reduction in MAO. We therefore have indirect evidence here that the early and late positive groups do not have the same secretory characteristics, as the 'recurrence' and 'no-recurrence' groups respectively. This accords with our finding of 4 cases of recurrence in the late positive group, differing in this respect from the findings of Ross and Kay.

The correlations of the means of the basals and MAO's with degrees of positive response are interesting but owing to overlap of the ranges are commonly of no help in the individual case.

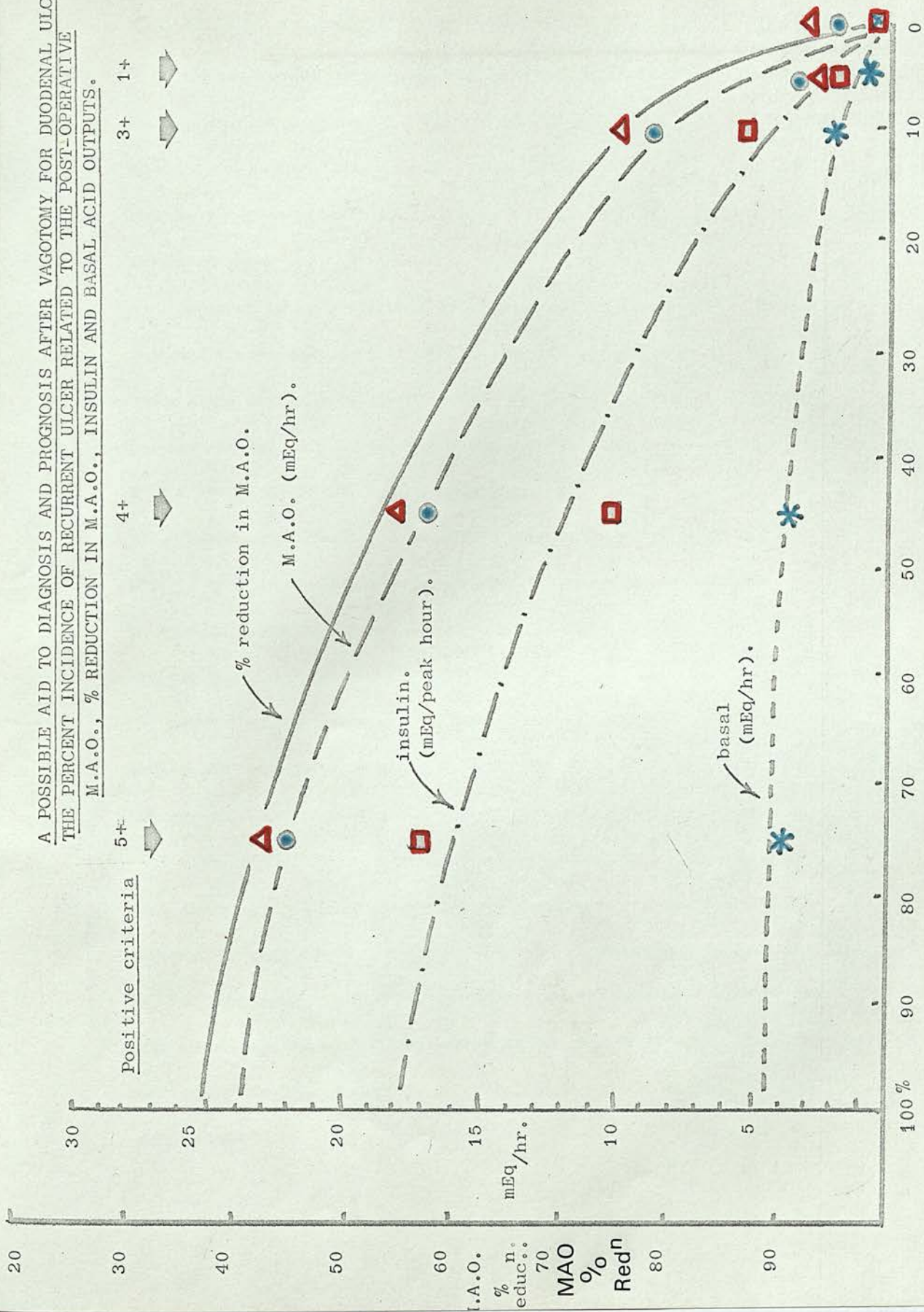
There is in fact no unanimity as to which tests are the most informative in investigation of peptic ulcer.

Figure III, 30 represents an initial attempt, derived from the data of this series, to provide the clinician with a guide to the probability of an individual post-vagotomy patient having, or developing, a recurrent ulcer.

It is based upon incidence of ulcer recurrence in insulin-negative patients and in categories 1, 3, 4 and 5 of the multiple criteria. There were insufficient data in the 2-positive category. Corresponding to each number of positive criteria (with its calculated incidence of recurrent ulcer) are plotted the means of the basal acid output (1-hour), IST (peak 1-hour),

/MAO

A POSSIBLE AID TO DIAGNOSIS AND PROGNOSIS AFTER VAGOTOMY FOR DUODENAL ULCER:
THE PERCENT INCIDENCE OF RECURRENT ULCER RELATED TO THE POST-OPERATIVE
M.A.O., % REDUCTION IN M.A.O., INSULIN AND BASAL ACID OUTPUTS.



PERCENT INCIDENCE OF RECURRENT ULCER.

(the secretory data have been grouped according to the number of positive criteria after insulin.)

MAO (1-hour) and per cent reduction in MAO. The presence of an early-positive response would shift the probability to the left.

Commonly the clinician has limited secretory data available. He could take any one or more of these parameters (and in practice he would usually have a basal plus either an IST or MAO) and derive an approximate indication of per cent probability of recurrence.

Application of data from individuals in our own series suggests that per cent reduction of MAO gives a better indication than absolute post-operative MAO but this pre-supposes routine pre-operative secretion tests on all patients and would limit the wider application of such a graph.

Sufficient data are already available from this series for many other interesting comparisons to be made. However a considerable volume of secretion studies carried out at this unit during the past decade is yet untapped. It is therefore proposed to defer further analysis until this information has been traced, and until time, by taking us nearer to the true incidence of recurrent ulcer, allows more exact correlations to be made.

The practical application of the material presented here is as follows. Firstly, the more strongly positive the post-operative secretory responses the more carefully must a patient be followed-up. Secondly we must ask ourselves whether the time has come that when the post-operative secretory data fall in the left half of the graph (i.e. greater than 50% chance of recurrent/

recurrent ulcer) we should admit that we have not treated the patient adequately and should propose elective re-operation.

Summary

1. With certain specific exceptions (Zollinger-Ellison Syndrome; suture-line ulcer) it is very unlikely that peptic ulcer recurs after complete vagotomy.
2. The Hollander Test has proved unsatisfactory in 2 respects: the dose of insulin recommended and the interpretation of the results. There is widespread disagreement upon both aspects.
3. Insulin both stimulates and inhibits gastric secretion. Together with the unpleasant symptoms of hypoglycaemia this fact demands that the smallest dose capable of eliciting a maximal or near-maximal insulin gastric secretory response should be used in the insulin test.
4. Studies in dogs using two different doses of insulin (0.15 and 0.6 u/kg.) demonstrated the higher dose to be a less effective stimulant due to a concurrent inhibitory effect. A small series of similar studies in patients using 0.15 and 0.3 u/kg. suggests the lower dose to be superior. The inhibitory effect of the higher dose by opposing a weak positive response may result in a 'false negative' result (Ch. 10).
5. The practice of performing routine pre-operative insulin tests at the Gastro-Intestinal Unit has provided the

/opportunity

opportunity to study the response to a dose of insulin much lower than has been reported elsewhere (0.1 u/kg.) in 165 non-operated patients (Ch. 13).

6. Insulin, 0.1 u/kg., produced a vigorous response in 96% of patients.

To avoid the 4% failure rate and yet preserve the advantages of the low dose, a sliding scale of 0.15 u/kg. has been adopted. The importance of monitoring the blood sugar is re-emphasised.
7. The mean peak 1-hour IST (using 0.1 u/kg.) was found to be 85% of the MAO. The mean highest concentration of acid during the IST was 97% of the mean highest MAO concentration.
8. In studying the post-operative response evidence is provided that the test performed within 2-3 weeks of operation may be unreliable.
9. A rise in volume after insulin is the commonest and the least useful criterion. A basal acid output of more than 2 m.Eq./hr. suggests incomplete vagotomy but this is not a uniformly reliable criterion.
10. Owing to its wide range the MAO; although showing good mean correlations with other criteria, is a less satisfactory index of vagotomy than the insulin response.
11. In interpreting the latter multiple criteria are recommended. In this series 50% of patients who had 3 positive criteria combined/

combined with an early positive, or 4 or 5 positives regardless of timing, had recurrent ulcer. Twenty-two out of 24 patients (92%) with recurrent ulcer had at least an early positive rise plus 3-positive criteria.

12. It is therefore suggested that the post-insulin response instead of simply being expressed as negative or positive should be expressed both in terms of the number of positive criteria and the timing of the response. Thus a '4 plus-early' would be recognised as having about a 50% risk of recurrent ulcer while a '2 plus-late' would virtually exclude the possibility.
13. A graph such as that shown in Figure III, 30, may also help the clinician in assessing prognosis or diagnosis.

PART IV

A Clinical Study of the Results of Vagotomy

CHAPTER 18THE RESULTS OF VAGOTOMY: INTRODUCTION

The follow-up of patients who have had gastric surgery, if it is to be efficient, requires secretarial assistance and social detective work of a high order. It is not surprising therefore that attempts to discover the true picture from the recent English language literature meet with frustration, despite the fact that the topic has been a popular one in surgical journals for many years.

A notable exception to the mediocre quality of the literature in this field is provided by the studies of Goligher and his colleagues (1968).

The obstacles, even in the small proportion of papers which provide detailed information, lie for example in the variable length of follow-up which must therefore influence the incidence of complications such as recurrent ulceration. Furthermore complications such as bilious vomiting, dumping and diarrhoea are difficult to define, especially the latter and even more difficult to compare between one author and the next.

Some of these complications will be discussed at greater length in following chapters. It is not proposed to attempt here

/an

an exhaustive review of the results of vagotomy since this information is available in a collective review very recently published by Williams and Cox (1969).

The physiological effects of vagotomy upon the biliary tract, pancreas, and small intestine will be summarised briefly in the chapter which deals with post-vagotomy diarrhoea.

The respective merits of truncal and selective vagotomy, currently hotly disputed among gastro-enterologists, are also analysed in respect of completeness of vagotomy.

Our controlled clinical trial of selective versus truncal vagotomy which has been running since May 1968 cannot yet be evaluated except in respect of certain practical aspects such as the points of technique, local anatomy or pathology which have influenced surgeons in accepting or refusing inclusion of a case in the trial and hence reflect on the practical role of selective vagotomy as a routine procedure. These aspects are discussed in Chapter 23.

The material in this section is derived from 345 patients who have been treated by vagotomy. These are not consecutive cases, nor do they represent all the material available in the unit. They represent the point currently reached in a continuing study which began as an inquiry into the results of selective vagotomy, subsequently widened to include truncal vagotomy and finally evolved into the construction of the controlled trial now in progress.

Methods of documentation were as follows. Information from case notes, including the nursing progress notes, temperature and fluid balance charts was transferred to proformata. These proformata were designed in such a way that information could be extracted by personal search or adapted to a computer programme. Until larger numbers accumulate it was decided to follow the former method. The data so compiled was transferred to punch cards (Copeland Chatterson, form C.C.14) from which the information included in this section was extracted manually. Examples of a proforma and master punch cards are shown in Appendix VI.

The follow-up of patients was accomplished almost entirely by personal interview. The author, either in conjunction with Mr. W.P. Small at his Gastric Surgery Follow-up Clinic or at a separate evening clinic, interviewed each patient. A small number who lived far afield replied to questionnaires and some who failed to report to the clinic were interviewed at home by Mrs. M. Colquhoun, Social Worker for the Gastric Follow-up Clinic. Patients who had their operation within the past eighteen months have been excluded from the long-term follow-up as being too recent for satisfactory evaluation.

A follow-up rate of 94% has been achieved in the remaining group of 260 patients.

/Much

Much is to be learned at this stage. For example our data upon the secretory studies after selective vagotomy are more comprehensive than anything published on this topic to date. The outcome of the controlled trial and correlations of secretory data with the development of recurrent ulcer must await further years of follow-up.

CHAPTER 19EARLY POST-OPERATIVE COMPLICATIONS OF VAGOTOMY

The relative safety of vagotomy as an operation for peptic ulcer is established. For example a recent series of 513 cases carried an operative mortality of 2 (0.4%) Goligher (1969). A remarkable feature of that series was the zero mortality in 233 operations involving gastric resection, a procedure found to carry a several times higher mortality by most reviewers (Schlicke 1963; MacDonald and Welsh 1965; Patterson 1965; Ohio Chapter, American College of Surgeons 1967). The relative safety of vagotomy is, in fact, sufficient to warrant its preference over partial gastrectomy as the operation of choice for duodenal ulcer. The correct choice of procedure to be combined with vagotomy is less clear.

It is the purpose of this chapter to discuss the operative mortality and morbidity of vagotomy.

Material and Methods

The results of 345 vagotomies performed during the past fifteen years have been examined. The incidence of operative complications in the main groups is shown in Table IV, 1. Information was obtained by retrospective scrutiny of case notes, nursing records and temperature charts and the methods of documentation have been outlined in the previous chapter.

/There

OPERATIVE AND EARLY POST-OPERATIVE COMPLICATIONS
OF VAGOTOMY IN 345 PATIENTS

Complication	T.V./DR. (137)	%	T.V./P.G. (68)	%	S.V./DR. (98)	%	S.V./P.G. (23)	%	V. alone (19)	%	Total	%
Splenectomy	1	-	1	-	0	-	0	-	0	-	2	0.5
Oesophageal Tear	1	-	1	-	0	-	0	-	1	-	3	0.9
Dysphagia	11	8	2	3	15	15	4	17	2	11	29	9
Ileus > 72 hrs.	6	-	4	-	5	-	4	-	1	-	14	4
Stomal Obstruction	10	7	2	3	1	1	0	-	0	-	13	4
Chest Infection	52	38	27	40	35	36	8	35	3	16	108	31
Pulm: Embolus	3	2	3	4	3	3	3	13	1	5	13	4
Wound Infection	14	10	9	13	9	9	2	87	4	21	38	11
Wound Dehiscence	3	-	1	-	1	-	0	-	0	-	5	1.4
Diarrhoea	62	45	26	38	27	27	9	39	3	16	129	37
Diarrhoea Severe	24	18	15	22	10	10	1	4	0	0	40	11
Deaths	0	-	0	-	0	-	0	-	0	-	0	-

DR. = Gastroenterostomy or pyloroplasty.
P.G. = Partial Gastrectomy.

TABLE IV, 1

There were no deaths in this series. In 2 cases damage to the spleen at operation necessitated removal of that organ. Minor oesophageal lacerations required suture in 3 cases. Dysphagia was a prominent post-operative complaint (9%), in some cases persisting for several weeks. In no instance did it result in permanent disability. Post-operative ileus necessitated nasogastric suction and intravenous fluid therapy for more than 72 hours in 4%, and it was usually associated with some other complication such as stomal obstruction.

In general it has been our policy not to prescribe antibiotics for patients with post-operative chest infections unless after twenty four hours they were failing to respond to physiotherapy. Therefore the cases included represent those for whom antibiotics were prescribed (31%). The incidence of pulmonary embolism (4%) is based on diagnosis by clinical examination, chest X-ray and electrocardiograph. Included under 'diarrhoea' are all those in whom it was recorded as a complication in the case notes, nursing record and charts. Patients in whom it was recorded as troublesome, for whom medical treatment was prescribed, and whose charts showed a frequency of more than 4 stools per twenty four hours have been listed as 'severe'.

Early and in some cases urgent re-operation was required in 4% of patients (Table IV, 2). Stomal obstruction necessitated revision of anastomosis in 3 patients after truncal vagotomy and
/gastroenterostomy

COMPLICATIONS NECESSITATING RE-OPERATION
AFTER VAGOTOMY

(345 Patients)

Complication	T.V./DR. (137)	T.V./P.G. (68)	S.V./DR. (98)	S.V./P.G. (23)	T.V. or S.V. alone (19)	Total (345)
Haemorrhage	1	0	1	0	0	2
Subphrenic Abscess	1	0	0	1	0	2
Stomal Obstruction	3	2	0	0	0	5
Wound Dehiscence	1	0	1	0	0	2
Empyema	1	0	0	0	0	1
					Total	12(4%)

TABLE IV, 2

gastroenterostomy and 2 patients after truncal vagotomy and partial gastrectomy. One patient bled severely from an oesophageal vein after selective vagotomy. Heavy intra-luminal bleeding followed gastroenterostomy and truncal vagotomy in one case. Two subphrenic abscesses were drained, two wounds needed re-suture and one patient required drainage of bilateral empyemata after multiple septic emboli, from an infected intravenous drip, led to lung abscesses.

The data are now to be divided in two different ways. Firstly a comparison is made between selective and truncal vagotomy and secondly between drainage and resection as accompanying procedures. Table IV, 3, expresses the results in two groups according to the type of vagotomy. Of the 19 patients who had vagotomy alone 3 were selective and the remainder truncal vagotomies, these are therefore added to the appropriate groups. It should be added that in 9 cases truncal vagotomy alone was performed because recurrent ulcer had developed after a previous gastroenterostomy (2 cases) or partial gastrectomy (7 cases).

Table IV, 4 compares the accompanying procedures, namely pyloroplasty (97 cases) gastroenterostomy (138) and partial gastrectomy (91 cases). The majority of pyloroplasties were of the Heineke-Mikulicz type. The Finney pyloroplasty was the alternative chosen where there was difficulty at the pylorus or duodenal bulb.

/Discussion

OPERATIVE AND EARLY POST-OPERATIVE
COMPLICATIONS OF TRUNCAL AND SELECTIVE
VAGOTOMY IN 345 PATIENTS

	Selective Vagotomy (124)	%	Truncal Vagotomy (221)	%
Splenectomy	0	0	2	0.9
Oesophageal Tear	1	0.8	2	0.9
Dysphagia	20	16.0	14	6.3
Ileus > 72 hrs.	9	4.0	11	5.0
Stomal Obstruction	1	0.8	12	5.5
Chest Infection	45	36.3	93	42.1
Pulmonary Embolism	6	4.8	7	3.2
Wound Infection	12	9.7	26	11.8
Wound Dehiscence	1	0.8	4	18.1
Diarrhoea:	37	29.8	90	40.7
Severe	11	8.9	39	17.6
Re-operation	3	2.4	9	4.1

TABLE IV, 3

OPERATIVE AND EARLY POST-OPERATIVE COMPLICATIONS:
COMPARISON OF PROCEDURES ACCOMPANYING VAGOTOMY

	Pyloroplasty (97 cases)	%	Gastro-Enterostomy (138 cases)	%	Resection (91 cases)	%
Splenectomy	1	1.0	1	0.7	1	1.1
Oesophageal Tear	0	0	1	0.7	1	1.1
Dysphagia	12	12.4	14	10.1	6	6.6
Ileus > 72 hrs.	5	5.2	6	4.3	8	8.9
Stomal Obstruction	1	1.0	10	7.2	2	2.2
Chest Infection	19	19.6	58	42.0	35	38.5
Pulmonary Embolism	3	3.1	3	2.2	6	6.6
Wound Infection	7	7.2	16	11.6	11	12.1
Wound Dehiscence	0	0	4	2.9	1	1.1
Diarrhoea	29	29.9	58	42.0	35	38.5
Severe	8	8.2	20	14.5	16	17.6
Re-operation	1	1.0	8	5.8	3	3.3

TABLE IV, 4

Discussion

These operations were performed largely by the same surgeons, in the same environment and with the same principles of post-operative care. The truncal vagotomies cover a period of 15 years, the selectives only 5 years. Prior to 1968 operations were selected for patients on the basis of the patient's age, sex and fitness, his or her maximal acid output, and the surgeon's preference. For these reasons, while some general comparisons may be permissible, statistical analysis is not appropriate.

Dysphagia after vagotomy has been described by a number of workers (Bruce and Small 1959, Schlicke 1963, Anderson 1966). Opinion is divided as to the cause. Oedema and inflammatory reaction may play a part in some cases, but a motility disturbance due to interference with the oesophageal innervation is probably the more significant factor. Thoracic vagotomy in dogs may produce an achalasia-like state and corresponding motility derangements have been demonstrated in humans (Harris and Miller 1960). This complication occurred more frequently after selective vagotomy in this series. In every case it resolved spontaneously, sometimes taking several weeks to do so.

Stomal obstruction, in our experience, is a common complication of gastro-enterostomy. It is less often seen after partial gastrectomy. It led to re-operation in 5 cases. The aetiology of this problem is not always clear and the fact that no case in

/the

the selective group has required re-operation for this cause suggests that denervation of the upper small bowel could play a role.

Other important complications that may be mentioned briefly are:-

1. Chest infections, which are showing signs of diminishing in number since subphrenic vacuum drains have been in regular use over the past two years.
2. Deep Venous Thrombosis and pulmonary embolism, hitherto under-diagnosed and treated with limited success are now being intensively studied in our patients undergoing abdominal operations. New methods of prophylaxis, diagnosis and treatment show signs of taming this bogey of major surgery.
3. Wound infections: the incidence of 11% in this series is an indictment of technique. The use of antibiotic solutions and wound vacuum drainage in selected cases is currently being studied in the Unit.
4. Diarrhoea appears to have been more of a problem in the truncal vagotomy patients in this series. The more important question of diarrhoea in the long-term follow up is discussed in the next chapter.

/Comparison

Comparison of the procedures which accompany vagotomy appears to show pyloroplasty in a favourable light in respect of chest infections and diarrhoea. These possible trends require confirmation in our controlled series. Gastro-enterostomy carried a high re-operation rate (5.8%) largely due to the problem of stomal obstruction.

Summary

It is concluded that vagotomy is a relatively safe operation. The introduction of selective vagotomy does not appear to have added to the morbidity, with the possible exception of an increase in transient post-vagotomy dysphagia.

CHAPTER 20LONG-TERM FOLLOW-UP AFTER VAGOTOMY

This chapter deals with follow-up material derived from 260 patients treated by vagotomy. The entire series at present available consists of 345 patients. Excluded from the present discussion are 67 who had their operation within the past eighteen months, since this is considered too short a time for worthwhile evaluation. Of the remaining 278 patients 260 have been traced by the methods outlined in Chapter 18. This gives a follow-up rate of 94%.

Division of cases into type of vagotomy and type of accompanying procedure together with the duration of follow-up of each group is given in Table IV, 5. It will be observed that the selective vagotomy group (87 patients) have a shorter mean duration of follow-up than the truncal vagotomies (173 patients). This reflects the fact that selective vagotomy was not performed in this unit prior to 1962.

Visick Grading

An overall assessment of the result of the operation and the capacity of the patient to enjoy a normal life is provided by the Visick (1948) classification. This recognises four categories of result (Table IV, 6). Categories I and II are regarded as highly satisfactory, category IV comprises the failures.

/Table

TYPE OF OPERATION AND DURATION OF FOLLOW-UP
IN 260 PATIENTS

Operation	Duration of Follow-up			Total
	2-5 Yrs.	5-10 Yrs.	>10 Yrs.	
T.V. & pyl.	16	12	1	29
T.V. & G.E.	39	32	6	77
T.V. & P.G.	25	32	7	64
T.V. alone	0	0	3	3
S.V. & pyl.	22	7	0	29
S.V. & G.E.	24	5	0	29
S.V. & P.G.	23	5	0	28
S.V. alone	1	0	0	1
TOTAL	150 (58%)	93 (36%)	17 (6%)	260

TABLE IV, 5

Table IV, 6

Overall Grading of Results: Modified Visick ClassificationFrom Goligher and Pulvertaft 1969

<u>Category</u>	<u>Definition</u>
I. Excellent	Absolutely no symptoms. Perfect Result.
II. Very good	Patient considers result perfect, but interrogation elicits mild occasional symptoms.
III. Satisfactory	Mild or moderate symptoms causing some discomfort, but patient and surgeon satisfied with result which does not interfere seriously with life or work.
IV. Unsatisfactory	Symptoms or complications which interfere with work or enjoyment of life; patient or doctor dissatisfied with result. Includes all patients with recurrent ulcer and all those submitted to further operation even though the latter may have been followed by symptomatic improvement.

Allocation of the patients in this series to Visick categories (Table IV, 7) shows that over 70% of all patients have a very successful outcome, a further 20% are satisfied although troubled with mild or moderate complications, and 7% have an unsatisfactory result.

Among the last group are 14 patients who underwent further surgery. Five had repeat vagotomies, 3 had gastric drainage replaced by partial gastrectomy - all for recurrent ulcer.

/Symptoms

ASSESSMENT OF RESULTS BY VISICK GRADING

Operation	Visick Grading				Total
	I	II	III	IV	
T.V. & pyl.	8	10	8	3	29
T.V. & G.E.	26	28	14	9	77
T.V. & P.G.	18	29	14	3	64
T.V. - Total	44(26%)	67(39%)	36(21%)	15(9%)	170
S.V. & pyl.	13	7	6	3	29
S.V. & G.E.	13	11	4	1	29
S.V. & P.G.	13	10	5	0	28
S.V. - Total	39(45%)	28(33%)	15(17%)	4(5%)	86
Over-all Total	91(36%)	95(37%)	51(20%)	19(7%)	256

TABLE IV, 7

Symptoms of stomal obstruction caused conversion of gastro-enterostomy to pyloroplasty in 2 cases and conversion from pyloroplasty to gastro-enterostomy in 2. All patients were improved by these conversions except one who after conversion from pyloroplasty to gastro-enterostomy continued to have bilious vomiting and was finally relieved by gastric resection. The vomiting of bile after truncal vagotomy and hemi-gastrectomy in two patients was treated by Roux-en-Y conversion with satisfactory results.

Two patients, both in the truncal vagotomy group, died during the period of follow-up. One male, age 35, committed suicide for reasons unrelated to peptic ulcer. The history of the other patient is instructive.

Mrs. J.A. (age 30) was admitted as an emergency with abdominal pain on 21/4/64. She gave an 11-year history of ulcer dyspepsia with recent vomiting. She was found to have a perforated duodenal ulcer. The perforation was closed and truncal vagotomy and gastro-enterostomy was performed by Mr. A. A. Gunn. A post-operative insulin test showed a 5+ response. On 20/12/65, because of persistent pain and vomiting she underwent re-vagotomy by Mr. W.P. Small; histologically-proven residual nerve fibres being found. A further post-operative insulin test was arranged but postponed because of the patient's holiday arrangements. Symptom-free she went on holiday to the Isle of Man in June 1966, only to be admitted to hospital with severe haematemesis. Emergency partial gastrectomy for stomal ulcer was performed by Mr. R. L. Lamming. Cardiac arrest occurred in the Recovery Room after apparently successful completion of the operation.

This death should be attributed to the failure to achieve complete vagotomy. Furthermore it is of interest that her 5-positive post-insulin response put her into what we should now recognise as the category with greater than 70% probability of developing recurrent ulcer.

Symptoms which tend to be troublesome after vagotomy are listed in Table IV, 8. Diarrhoea is considered as a separate subject in Chapter 21. Flatulence is a common complaint among these patients. Dumping, usually of the early variety, occurs in the majority of patients regardless of whether drainage or resection has been performed. It generally subsides within twelve months of operation, assisted by minor adjustments to diet. The 11% represent those in whom dumping remained troublesome. Conversion to an interposed jejunal segment (provided the vagotomy is complete) should perhaps be considered more often for this unpleasant complaint. Biliary vomiting after gastro-jejunostomy or Polya gastrectomy and the vomiting of food or bile sometimes seen after pyloroplasty, when persistent or when coming on late after a period of post-operative freedom from trouble, are mechanical problems best dealt with by conversion to the alternative drainage procedure, to a Bilroth I anastomosis or to a Roux-en-Y type of anastomosis.

Abdominal pain after vagotomy was of two types. In the patients with incomplete vagotomy recrudescence of epigastric pain spelt recurrent ulcer. There was also a colicky central abdominal pain, often associated with borborygmi and distension - what American authors describe as 'cramps with bloating'. This pain is unrelated to recurrent ulcer and probably represents a disturbance of motility.

/Recurrent

POST-VAGOTOMY SYMPTOMS

	Selective Vagotomy (86 cases)	Truncal Vagotomy (170 cases)	S.V. + T.V. (256)
Flatulence	9(10.4%)	38(22.4%)	47(14.8%)
Dumping	4(4.7%)	25(14.7%)	29(11.3%)
Bile or food vomiting	7(8.1%)	15(8.8%)	22(8.6%)
Symptoms of reflux	5(5.8%)	14(8.2%)	19(7.4%)
Pain	4(4.7%)	12(7.1%)	16(6.3%)
Loss of weight	7(8.1%)	44(25.9%)	51(19.9%)
<u>Recurrent Ulcer</u>			
Suspected	1(1.2%)	17(10.0%)	18(7.0%)
Proven	3(3.5%)	10(5.9%)	13(5.1%)

TABLE IV, 8

Recurrent Ulcer, either proven at operation or strongly suspected on evidence of pain or haemorrhage, occurred in 31 (12.1%) of patients. Three of these patients had selective vagotomy. It is too early to assess the latter group fully in this respect. The secretory characteristics of patients with recurrent ulcer are discussed in Chapter 17.

Change of weight with operation is particularly difficult to assess. Post-operatively each patient was weighed when he or she attended the follow-up clinic. If the patient was unable to state what his best pre-operative weight had been the highest recorded pre-operative weight was taken from the ward chart.

The all-important question of whether selective vagotomy provides any advantage over truncal vagotomy is not resolved by these figures. The apparent superiority shown by the selective operation in Tables IV, 7 and 8 required confirmation by controlled trial. Although much has been written on selective vagotomy only three trials have been published. (Sawyers, Scott, Edwards, Small and Law 1968; Mason, Giles, Graham, Clark and Goligher 1968; Kennedy and Connell 1969). These authors do not find any significant difference between truncal and selective vagotomy in respect of post-operative complications. It must be pointed out however that such has been the haste to publish in this controversial field that the average follow-up in these three series is one year. This we believe to be less than adequate. The question remains open.

/Conclusions

Conclusions:

Vagotomy is an operation with a gratifying success rate and a low mortality rate. At this stage in our series selective vagotomy appears in a favourable light but the comparison with truncal vagotomy requires more rigid control combined with long-term follow-up.

Comment is required upon the high incidence of recurrent ulcer in this series (12.1%). By definition this figure includes both 'suspected' and 'proven' cases. The latter group comprises 51%. It is our belief that longer follow-up of vagotomy and drainage will reveal an incidence of recurrent ulcer of greater than 10% until a general improvement in the technique of vagotomy is achieved.

CHAPTER 21DIARRHOEA AND THE PHYSIOLOGICAL EFFECTS OF VAGOTOMY

The cause of diarrhoea after vagotomy is still an enigma.

The existence of the problem, denied in some quarters and exaggerated in others, is acknowledged by those who have studied the question carefully (references: page 5). An exhaustive critical evaluation of the evidence was provided by Cox and Bond (1964). They concluded that the incidence of persistent and troublesome diarrhoea after vagotomy was about 5%.

Post-vagotomy diarrhoea may be sufficiently troublesome for some authors to recommend that truncal vagotomy should not be performed for conditions which can reasonably be treated by an alternative operation. In a series of 87 patients with hiatus hernia treated by truncal vagotomy and pyloroplasty, Pearson and co-workers (1969) found 7% were dissatisfied with the result of the operation because of diarrhoea. Significantly the authors remarked that the overall incidence of dissatisfaction because of either diarrhoea or dumping (9%) was greater than dissatisfaction because of recurrent symptoms of gastro-oesophageal reflux.

Truncal vagotomy cannot be justified as a treatment of hiatus hernia unless hyperacidity and/or duodenal ulcer disease are also present.

Disagreement about what is meant by the term 'diarrhoea' holds many discussants apart. Any review therefore requires careful

/definition

definition of terms. Little information is available about bowel habit before vagotomy thus making more difficult the assessment of post-operative changes. Certainly the ingestion of antacids and other medications may promote either constipation or diarrhoea.

Standardisation of follow-up information is important.

Barnes and Cox (1969) provide a useful classification of the types of bowel change encountered:-

- (a) Increased daily bowel frequency - the majority of patients regard this as a very satisfactory bonus.
- (b) Transient diarrhoea begins early after operation and lasts for no more than a few weeks or months. This group was mentioned in Chapter 19.
- (c) Episodic diarrhoea - bouts of diarrhoea interrupt an otherwise regular bowel habit. Intervals vary from a few days to several weeks. A typical attack starts without warning and lasts for a few hours to one or two days during which time many liquid stools are passed often with extreme urgency or even incontinence. Many large series contain one or two cases where the patient is socially incapacitated by such attacks.
- (d) Constipation develops in a few patients after vagotomy.

Diarrhoea was the chief spur to the introduction of selective vagotomy. Enthusiasts for this operation have claimed a decreased incidence and particularly a reduction in severity of diarrhoea

/(Burge

(Burge 1960; Griffiths, Stavney, Kato and Harkins 1963; Tanner 1965; Hyde and Hull 1965; Hedenstedt and Lundquist 1966). Where an attempt has been made to assess selective vagotomy on a controlled trial basis a significant difference has not been shown (Sawyers, Scott, Edwards, Shull and Law 1968; Mason, Giles, Graham, Clark and Goligher 1968; Kennedy and Connell 1969).

As noted in the foregoing chapter the follow-up in these latter studies is short and further information from controlled series is certainly needed. It is the purpose of this chapter to review the results of long-term follow-up in 256 patients.

Results

The information sought at the follow-up interviews is shown on punch card 2 in Appendix VI. It will be appreciated that precise information was often difficult to obtain and the distinction between moderate and severe diarrhoea was particularly difficult in some patients. For example, the number of stools per day is not necessarily the best criterion since in some patients the main problem was precipitancy of the call to stool. General principles were that 'diarrhoea' was defined as the passage of three or more loose stools in 24 hours, 'severe diarrhoea' was defined as being sufficient to interfere with everyday life and work.

Table IV, 9(a) sets out the results in this series. 61% of post-vagotomy patients have a change in bowel habit in the direction of increased frequency. Most regarded this as an improvement, an

/effect

BOWEL HABIT AFTER VAGOTOMY

	No Change	Change in Frequency	Diarrhoea		Total
			Mild/Mod:	Severe	
T.V. & pyl:	12	17	8	1	29
T.V. & G.E.	35	42	14	5	77
T.V. & P.G.	16	48	23	4	64
T.V.: Total	63(37%)	107(63%)	45(26%)	10(6%)	170
S.V. & pyl:	14	15	10	0	29
S.V. & G.E.	13	16	7	0	29
S.V. & P.G.	10	18	4	0	28
S.V.: Total	37(43%)	49(57%)	21(24%)	0	86
Over-all Total	100(39%)	156(61%)	66(26%)	12(5%)	256

TABLE IV, 9 (a)

effect of the operative for which many expressed gratitude. Mild to moderate diarrhoea was observed in 26% and this was almost invariably episodic in type.

A 5% incidence of severe diarrhoea occurred entirely in the truncal vagotomy group. Table IV, 9(b) shows the reviewed incidence of diarrhoea in the two types of vagotomy.

Diarrhoea and the Completeness of Vagotomy

The patients were divided into those whose post-operative insulin test was positive (46) and those in whom it was negative (113). Satisfactory insulin tests were not available in the remaining 97. No significant difference in incidence or severity of diarrhoea could be detected between the two groups. Two patients who had incomplete truncal vagotomies were in the 'severe' diarrhoea group.

Discussion

While confirming post-vagotomy diarrhoea as an entity, we have not advanced knowledge of its cause. Advocates of selective vagotomy favour this operation in order to preserve the parasympathetic innervation that the vagi carry to the fore-gut, mid-gut and their derivatives. What do we know of the physiological functions of these distal vagal fibres, and what happens to the digestive tract when they are divided?

/The

DIARRHOEA AFTER VAGOTOMY

Date	Author	No.	T.V. % Diarrhoea	No.	S.V. % Diarrhoea
1963	Griffiths	-	-	55	'no troublesome diarrhoea'
1963	Kraft*	40	38%	40	19%
1963	Farris	-	-	40	'50% reduction'
1965	Hyde	-	-	21	5%
1966	Hedenstedt	-	50%	50	8%
1966	Tanner	-	25%	47	7%
1967	Williams*	43	9%	22	0%
1968	Burge	-	30%	300	'no troublesome diarrhoea'
1968	Mason*	52	33% (severe 9.6%)	60	20% (severe 0%)
1968	Sawyer*	86	21%	48	13%
1969	This series	170	32% (severe 5.0%)	86	24% (severe 0%)
		Mean	31%	Mean	13%

(*trial)

TABLE IV, 9 (b)

The vagal pathways are complex. The main trunks in the abdomen are approximately 90% amyelinate and 90% afferent, and they contain an admixture of approximately 10% of sympathetic fibres (Kuntz 1946). Most authors believe the nerves are preganglionic until they reach the intrinsic ganglia of the digestive organ such as the myenteric and submucosal plexuses of the small intestine. This view has recently been challenged by Keen (1966) who believes that many of these fibres have a relay in the vagal ganglia at the base of the skull.

Iggo has succeeded in stimulating isolated afferent and efferent (1967) vagal fibres. He studied motor effects. Other studies, and there are many, have involved examination of relatively gross physiological function before and after division of compound vagal trunks, electrical stimulation of divided trunks or chemical stimulation of intact ones in man or in animals.

Our knowledge of how the vagal neuron reaches its end-organ is imprecise. The intermingling of sympathetic with parasympathetic fibres and the difficulty of following nerves through the matted coeliac and superior mesenteric plexuses have set severe limitations upon our visual pursuit of distal vagal pathways. The vagi in man comprise a mean of approximately 57,000 fibres at their point of entry into the abdomen (Hoffmann and Schnitzlein, 1961). The discrepancy between this relatively small number and the many structures supplied and functions subserved is an indication of the

/important

important role of the internuntial neurons and multipolar ganglia of the gastro-intestinal tract. The distribution and even the enumeration of the cells in the myenteric and submucosal plexuses of the small intestine has been described (Sauer and Rumble 1946, Richardson 1960) and there is information concerning both stimulatory and inhibitory transmitter substances at muscular and mucosal nerve endings (Bulbring 1961; Bulbring and Gershon 1968).

Divers information such as this has yet to marry knowledge of structure with function as far as the aetiology of post-vagotomy diarrhoea is concerned. The following paragraphs summarise the experimental evidence for the importance of extrinsic parasympathetic nerves in the function of the digestive organs.

1. The Biliary Tract

The gall-bladder and biliary tree are endowed with a rich intramural network of parasympathetic ganglionic nerve fibres (Burnett, Gairns and Bacsich 1964).

Severence of the vagi has been reported to result in progressive dilatation of the gall-bladder as measured radiologically by several workers (Johnson and Boyden 1952; Cox, Doherty and Kerr 1958). Glanville and Duthie (1964) were unable to demonstrate any changes in gall-bladder size after vagotomy.

/Information

Information upon the rate of emptying of the gall-bladder after vagotomy is less clear. It is generally agreed that cholecystokinin is the principal stimulant of gall-bladder contraction. On theoretical grounds some interference with the timing of gall-bladder emptying might be expected after vagotomy. The picture is complicated by the fact that cholecystokinin release is influenced by gastric emptying. Therefore the apparently conflicting results as reviewed by Rendall and Silen (1969) can be explained by the varied gastric drainage procedures accompanying the vagotomy. For this reason Glanville and Duthie (1964) timed the rate of gall-bladder emptying from the time of entry of food into the duodenum and found no change after vagotomy.

Whether the dilatation of the gall-bladder or other effects, as yet conjectural, such as for example an interference with vasomotor control, is capable of disturbing the physico-chemical equilibrium of bile is still not clear. Evidence is circumstantial and conflicting. An increased incidence of gall-stones after vagotomy has already been mentioned, (Page 5). The reports lack proof. An interesting experiment was reported by Hilbrun and Barnett (1965) who showed that human gall-stones were dissolved when introduced into the canine gall-bladder. The performance of selective vagotomy did not change this effect but after truncal vagotomy the stones failed to dissolve. In the rabbit, truncal

/vagotomy

vagotomy results in reduced tonus and a reduced ability to concentrate bile (Freeston and Bouchier 1968). Using the lithogenic agent dihydrocholesterol introduced into the diet these workers failed to show any increased incidence of gall stones after truncal vagotomy.

Reflex relaxation of the sphincter of Oddi is thought to be vagally mediated. Division of the hepatic branches of the anterior vagus has therefore been recommended as a means of reducing pressure within the common bile duct after biliary surgery (Schein and co-workers 1969).

2. Vagotomy and the Pancreas

The diarrhoea which follows vagotomy is not always a steatorrhoea. However, as Burge (1964) has stressed, many patients report the passage of stools which are paler as well as more frequent than before operation, and many authors have demonstrated increased levels of faecal fat after truncal vagotomy (Fox and Grimson 1950; Butler 1960; Cox, Bond, Podmore and Rose 1964; Butler and Eastham 1965; Wastell and Ellis 1966; Craft and Venables 1968). A direct relationship between the impaired fat absorption and diarrhoea has not been demonstrated (Kraft, Fry and Ranson 1962; Logan 1964; White, Lenninger, Elmslie and Magee 1966; Williams and Irvine 1966; Dellipiani and Girdwood 1967).

The most potent stimulants of pancreatic secretion are secretin and pancreozymin. The extrinsic innervation, however, does have a role to play both directly and indirectly. Electrical

/ stimulation

stimulation of the central portion of the divided vagus in the anaesthetised cat was found to provoke an output of pancreatic juice rich in enzymes (Harper, Kidd and Scratcherd 1959) thereby confirming Pavlov's postulate of a 'cephalic phase' of pancreatic secretion. An indirect gastrin-mediated mode of vagus-stimulated secretion is strongly suggested by a pancreatic response to gastric distension (White, Lundh and Magee 1960; Brooks and Manfredo 1964) and to sham-feeding in the presence of a vagally-innervated antral pouch (Preshaw, Cooke and Grossman 1965). Preservation of the vagal fibres to the pancreas by selective vagotomy in dogs was found to result in a secretory response occurring within the first 30 minutes after a meat meal while the response after truncal vagotomy was delayed for more than 30 minutes (Govaerts and Kiekens 1968). These authors therefore conclude that the vagus is important in the early phase of the pancreatic response to food.

Evidence that vagotomy interferes with pancreatic secretory volume on enzyme output is conflicting. The pancreatic secretory response to insulin is abolished by truncal vagotomy in man, dog and rat (Dreiling, Druckermann and Hollander 1952; Pfeffer, Stephenson and Hinton 1952). These authors reported a reduced volume response as well as a fall in enzyme output suggesting that there was a reduced release of secretin secondary to lowered acidity of gastric juice entering the duodenum (Cox 1969). A significantly greater fall in the daily volume and enzyme output of pancreatic juice in dogs was found after truncal vagotomy than

/after

after selective vagotomy by Lenninger, Magee and White (1965) but a similar effect could not be confirmed in dogs (Bastable 1965) nor in humans (White, McAlexander and Magee 1966). Lenninger and colleagues also showed a depressed response to secretin after truncal vagotomy. In man Pfeffer, Stephenson and Hinton (1952) found reduced volume flow and bicarbonate concentration after vagotomy. Other workers failed to demonstrate this reduction. The volume, bicarbonate and enzyme response to a standard meal introduced by tube into the duodenum was found by Butler (1960) to be reduced in man after vagotomy, but Holmquist and Colleen (1965) did not find a significant change during the two hours following the ingestion of a standard meal. Fields and Duthie (1965) showed that the amounts of lipase and bile acids in the intestinal lumen were diminished after truncal vagotomy.

Thus it will be observed that we remain in doubt as to whether the function of the pancreas is substantially impaired by truncal vagotomy. It seems most probably that the fault is one of timing. The precipitate emptying of the stomach known to occur after gastric operations, especially in the presence of a gastrojejunostomy, and the abolition of the cephalic phase of pancreatic secretion probably combine to produce defective mixing of food with bile and pancreatic juice.

3. Vagotomy and the Intestine

(a) Motility - It has commonly been taught that vagotomy may

be

/be

be followed by a prolonged adynamic ileus, and while it is true that after operations for duodenal ulcer there is sometimes abdominal distension, with depressed or inaudible bowel sounds for two or more days, studies upon post-vagotomy patients in this series using a telemetering capsule inserted at operation showed that in some cases pressure activity did not cease at all after operation, and in the majority it had returned within six hours. Initial pressure patterns were incoordinate but integrated propulsive activity could generally be demonstrated within 24 hours (Smith and Ridgeway 1962). Similar findings were reported by Ross, Watson and Kay (1963).

Radiological changes have been reported later after vagotomy. Dilatation, flocculation and pooling of barium have been observed in a series of barium studies performed upon 83 patients at intervals up to six months after vagotomy and drainage. The passage of barium through the small bowel was consistently delayed (Isaac, Ottoman and Weinberg 1950). Roth and Beams (1959) found no delay in the passage of barium, and using manometric balloon tracings the only difference after vagotomy was an increased frequency of type III waves. These differences may simply have reflected different rates of gastric emptying. Accelerated small intestinal transit after vagotomy has been reported by Collins, Crile and Davis, 1948; Waddell and Wang 1952/53 and Madsen and Pedersen 1968. The successful use of an
/antiperistaltic

antiperistaltic segment of jejunum for the treatment of post-vagotomy diarrhoea has been described by Craft and Venables (1968).

(b) Intestinal Mucosa - The villi of the small intestine in the dog were found by Ballinger (1963) to show degenerative changes after vagotomy. These changes, however, were transient, the mucous membrane returning to normal within eight months. Further studies related these changes to decreases in mucosal content of alkaline phosphatase, acid phosphatase, succinic dehydrogenase and non-specific esterase and to a rise in bacterial colonisation (Ballinger, Iida, Wirts and Goldstein 1964). The changes occurred after both truncal and selective vagotomy. Other groups were unable to confirm these findings in the dog (Elliot, Barnett and Elliot 1967), or in the rat (Ellis and Pryse-Davies 1967).

A mean fall of 42% in mesenteric blood flow as measured in the common mesenteric vein after vagotomy was observed in an acute experiment in dogs by Ballinger, Padula and Camishon (1965). There does not appear to be any information in the literature upon the long term effects of vagotomy upon blood flow to the bowel.

By labelling dividing mucosal cells with tritiated thymidine Silen, Peloso and Jaffe (1966) demonstrated in biopsies taken from Thiry-Vella fistulae in dogs that the epithelial turnover at six weeks after vagotomy was significantly accelerated. This change may reflect abnormal bacterial colonisation since there is

/a

a relationship between cell renewal and bacterial flora in the bowel (Duthie 1965),

Estimations of the levels of urinary indican, a metabolite reflecting small-intestinal bacterial activity, in our unit and elsewhere (Barnes and Cox 1969) have so far failed to correlate with episodes of diarrhoea.

Very little work has been done to measure directly the effects of vagotomy upon absorption from the bowel. This aspect has been reviewed by Cox (1969) who concludes that there is no evidence of significant change after vagotomy.

Conclusions

Thus the cause of post-vagotomy diarrhoea remains conjectural. There is probably sufficient in the reviewed evidence of disturbed pancreatic function, accelerated gastric emptying and intestinal transit time to account for moderate change in bowel habit in terms of impaired mixing of food and enzymes aggravated by intestinal hurry.

To account for the cyclical, sometimes severe, diarrhoea a different mechanism must be invoked. The likeliest would appear to be related to bacterial colonisation, but there is no evidence available as yet to prove a relationship (Dellipiani and Girdwood, 1967; Barnes and Cox, 1969).

When considering the value of selective vagotomy in avoiding this complication, the shortcomings of other evidence in this

/ field

field have already been outlined. The material presented from our own series is not exempt from similar criticism. It can be stated at least that while selective vagotomy fails to provide immunity from diarrhoea we have yet, in over 140 cases, to see an example of persistent severe diarrhoea. There is, however, no clear difference in overall incidence between the two groups. We therefore conclude, with Tanner (1966), that we may be witnessing a reduction in severity rather than incidence of this complication and await with interest the outcome of longer follow-up of these patients.

CHAPTER 22COMPLETENESS OF VAGOTOMY

The object of vagotomy is to cure peptic ulcer. Failure to do so may result in physical disability, economic loss and the discomfort, morbidity and possible mortality attendant upon re-operation. Surgery for recurrent ulcer can be technically difficult and may sometimes be required as an emergency because of haemorrhage. Should the surgeon consider partial gastrectomy to be necessary in such circumstances the operative risk rises dramatically, and the case of Mrs. J. A., described in Chapter 20, illustrates this point only too well.

The incidence of incomplete vagotomy generally quoted, ranging between 10 and 40% and averaging approximately 30%, is probably a serious underestimate. Reasons for this statement are several. Firstly the figures are provided by groups sufficiently interested in the problems of vagotomy to carry out frequent post-operative tests. Such groups are likely to be more, rather than less, successful than the average in performing efficient vagotomy. Secondly there is a widespread misconception, fostered by most textbooks on the subject, that truncal vagotomy merely consists of division of an anterior and posterior (or left and right) vagal trunk. As our anatomical studies (Chapters 2 and 3) have shown, if the surgeon contents himself with division of two trunks, he will have an incomplete vagotomy rate exceeding 50%. Thirdly the figures for incomplete vagotomy are

based

based upon tests, and interpretations of tests, which are highly questionable. This aspect has been discussed at length in Part III. Fourthly many published series include tests performed after vagotomy plus partial gastrectomy. The extent to which such tests may be misleading has been discussed in Chapters 7 and 8.

Superior results have been claimed for selective vagotomy in respect of 'completeness' of gastric denervation. The results of our own series are analysed in this chapter. Selective and truncal vagotomy are compared. The influence of surgical technique and the surgeon's experience are examined. The principles of successful vagotomy are re-emphasised.

Materials and Methods

Post-operative insulin tests were carried out on a total of 249 patients during this period. The method of performing these tests has been described in Chapter 12. The principles underlying the exclusion of tests performed in the early post-operative period and of tests of dubious validity have also been outlined (Chapter 13). We therefore have for analysis 139 post-operative tests, performed between two months and 15 years after operation. They comprise 103 after vagotomy and drainage and 36 after vagotomy and resection. In interpreting the tests multiple criteria have been used as discussed in Chapters 12-17. Tests are classified as positive if they showed three or more positive criteria. This has resulted in classifying as negative seven tests positive by Hollander's criteria and as positive four tests

/which

which were negative by Hollander's criteria. Had the criterion of an early-positive rise been applied, as advocated by Ross and Kay (1964), fourteen tests would have been classed as negative which are in fact regarded here as positive. These points underline the difficulty of comparing results from different centres.

Results:

The overall results in 139 tests divided according to operation are shown in Table IV, 10. The effect of antral resection as evidenced by the difference in positive results between vagotomy with drainage (37%) and vagotomy with resection (14%) has been discussed earlier (Chapters 7 and 8).

The incidence of incomplete vagotomy of 44% after truncal vagotomy with drainage compares with that of 30% after selective vagotomy and drainage. No such difference was apparent between truncal and selective vagotomy when combined with resection. The effects of antrectomy and also the small numbers involved make interpretation difficult in the latter group.

An attempt has been made to study the influence of technique and experience upon the outcome. The results in the vagotomy and drainage group (103 cases) have been divided according to the surgeons (Table IV, 11). The range of incomplete vagotomy

/varies

RESULTS OF INSULIN TESTS AFTER VAGOTOMY IN 139 PATIENTS

Operation	Negative	Positive	Total
T.V. & DR:	28	22(44%)	50
S.V. & DR:	37	16(30%)	53
Total DR:	65	38(37%)	103
T.V. & RES:	21	3(13%)	24
S.V. & RES:	10	2(17%)	12
Total RES:	31	5(14%)	36
Over-all		43(31%)	139

DR: = Gastro-jejunostomy or pyloroplasty.

RES: = Partial gastrectomy.

TABLE IV, 10

RESULTS RELATED TO SURGEON (103 CASES)

		No. of Cases	% of Total	I.S.T. + ves.	% Positive
<u>CONSULTANT SURGEONS</u>	1	13	12.5	3	23
	2	11	10.5	5	45
	3	27	26	6	22
	4	5	} 8	2	-
	5	2		1	50
	6	1		1	-
<u>JUNIOR STAFF</u>	7	11	10.5	7	64
	8	17	16	3	18
	9	6	} 16	4	} 65
	10	3		3	
	11	2		0	
	12	2		1	
	13	1		1	
	14	1		1	
	15	1		0	
	Total	103		Total 38	Mean 37%

TABLE IV, 11

varies between 18% and 64%. Table IV, 12, compares the same data taking simply the results of the three consultant surgeons who between them performed 59 (57%) and members of junior staff who had each performed less than 10 vagotomies; 17 cases (16.5% of the series). The figures for incomplete vagotomy are 27% and 65% respectively.

That the study of the vagal anatomy results in more satisfactory vagotomy is shown by a personal series of 46 vagotomies (39 selective, 7 truncal). In 5 vagotomy was combined with gastric resection. Of the remaining 41 late post-operative secretion tests are available in 17, of which 3 are positive by multiple criteria, an incidence of 18%.

We have evidence from another source that heightened interest in the problem results in better vagotomy. Table IV, 13, shows the outcome of 73 late post-operative insulin tests (omitting those done on suspicion of recurrent ulcer) after operations done before and after 1967 by the four surgeons who have done the majority of the cases in this series. A striking fall in the incidence of positive tests is demonstrated, from 30% in the earlier group to 10% in the recent group. In the personal series quoted above all the positive tests followed operations done in the first half of the series.

/Discussion

THE INFLUENCE OF EXPERIENCE UPON SUCCESSFUL VAGOTOMY

(68 Cases)

	No. of Cases	No. of +ve tests	% Incomplete
Consultant Surgeons (3 Surgeons)	51	14	27%
Junior Staff (8 Surgeons)	17	11	65%
'Junior surgeons' as a group comprise those who have each done less than 10 vagotomies in this series			

TABLE IV, 12

THE RESULTS OF VAGOTOMY BEFORE AND AFTER 1967

Surgeon	Pre-1967		Post-1967	
	Positive	Negative	Positive	Negative
A	2	7	0	4
B	5	3	2	3
C	4	13	0	6
D	2	8	1	13
Total	13(29.5%)	31	3(10.3%)	26
	44		29	

TABLE IV, 13

Discussion

A disturbingly high incidence of incomplete vagotomy is demonstrated by this review. Some of the reasons why the insulin test as we perform it may provide a higher percentage of positive results than other reported series are discussed in Chapters 10, 12 and 13. It was stated in Chapter 12 that our policy has been to perform 'routine' post-operative insulin tests. We have here a series of 345 patients but have been able to make use of only 139 out of 249 tests for this analysis. In addition to the fact that to perform follow-up tests on all patients after their discharge from hospital is impossible it is apparent that much effort, time and expense have been expended upon tests performed at the wrong time or with imperfect technique. Despite recognition that this series does not represent 'routine' follow-up studies and also that it is 'loaded' by a proportion of patients who returned to the orbit of the follow-up clinics expressly because they developed recurrent symptoms the incidence of incomplete vagotomy is still disturbingly high. How is it to be reduced?

No satisfactory method of testing for completeness of operation yet exists. The Burge machine (Burge and Vane 1958), which demonstrates vagal motor function manometrically after electrical stimulation of the electrode - encircled oesophagus, in our hands has been fraught with technical difficulty and

/inaccuracy

innaccuracy. For example a wide range of drugs such as anticholinergics and many commonly used anaesthetic agents will nullify the test. Lythgoe (1961) carried out a trial of the Burge machine in 25 patients and found 3 false negative responses to stimulation even before vagotomy had been started! He pointed out that the anatomic situation of the posterior trunk, separated as it is by some distance from the oesophagus in many cases, makes it liable to be missed by the encircling electrode.

Currently under trial in this unit is the leucomethylene-blue (Panatone; Paines and Byrne Ltd.) stain for vagal fibres. This may be of some help but it should be pointed out that leucomethylene blue stains connective tissue as well as nerve fibres.

There is no substitute for the careful scrutiny of the well-exposed, and well-illuminated oesophagus under direct vision; with circumcision of all visible and palpable connective tissue, vascular and nerve fibres together as they lie on and among the longitudinal muscle fibres of the lower oesophagus. The results of the more recent cases in this series (Table IV, 13) suggest that substantial improvement can be made. Selective vagotomy should not be superior to truncal vagotomy in this respect, for this meticulous technique should be common to both.

We are currently carrying out selective vagotomy without any drainage procedure in patients who have no radiological evidence of pyloric obstruction, who show no delay in a pre-operative

/phenol

phenol-red dilution gastric emptying test and who do not have obvious pyloric obstruction observed at operation. The rationale for this procedure is that preservation of anterior vagal branches to pylorus and duodenum may avoid post-vagotomy gastric retention. The initial results are encouraging. It is mandatory for such an operation however that the surgeon must have confidence in his ability to perform a good vagotomy.

It should not be thought that superior technical ability is claimed as necessary for successful vagotomy. Increased interest in the problem, especially the anatomy, brings appreciation of what is required. The necessary technique is well within the compass of every abdominal surgeon. Neither should the demonstration of more satisfactory results by experienced surgeons mean that this operation should not be the province of the trainee. It means simply that the vagotomy performed by the inexperienced surgeon must be scrupulously checked at operation by his mentor.

In the introduction to this section the hope was expressed that these studies would encourage more effective application and better interpretation of the insulin test in post-operative patients. Such is the stimulus to surgeons when they are presented with an audit of their results that the dividend in terms of a better patient-care both at operation and as a result of efficient organisation of follow-up services far outweighs the

/work

work involved in such a study. Above all it has served to emphasise the fact that without controlled trials of these controversial operations final and objective assessments cannot be made.

CHAPTER 23PRELIMINARY OBSERVATIONS ON A TRIAL
OF TRUNCAL AND SELECTIVE VAGOTOMY

A special survey of operations for duodenal ulcer was instituted at the Western General Hospital early in 1968. This survey has included a trial of selective versus truncal vagotomy and of gastroenterostomy versus pyloroplasty. To these alternatives patients have been allocated on a controlled randomised basis.

The trial is running satisfactorily at the present time and it is of course too early to assess any long term clinical results. It is proposed, in this chapter, to analyse the factors which have influenced surgeons in their willingness to accept random selection for their patients. Upon such considerations may depend the future role of selective vagotomy.

It was stated in Chapter 3 (Page 53) that the observed anatomical variations did not preclude the application of a standardised technique to the operation of selective vagotomy. On the other hand, this may be a difficult operation in the presence of anything which narrows or obliterates the area between stomach, left lobe of liver and diaphragm, or the lesser sac or in the presence of an anatomical abnormality such as an aberrant left hepatic artery arising from the left gastric pedicle.

If an operation is rejected for technical reasons in a large number of cases, by surgeons with a special interest in the field, it can scarcely be a strong candidate for universal acceptance.

/Construction

Construction of the Trial

It was felt to be important from the outset that a trial such as this should be sufficiently flexible to allow for differences in surgical skill and experience. The surgeon must feel free to withhold a particular patient from the trial if he so desired. It was decided to allow a choice of trial options at two stages in the operation, one for the type of vagotomy and the second for the type of drainage. Thus a surgeon could draw an option on the vagotomy but elect not to do so for the drainage procedure and vice versa. This also allowed the inclusion of vagotomy alone and vagotomy with antrectomy in the trial. A proforma was drawn up for completion by the surgeon or his assistant. An example is shown in Appendix VI.

The point in time at which a surgeon should decide whether to draw an option was also important. For the vagotomy it was felt that this decision should be deferred until stomach and lower oesophagus had been exposed, in order that the surgeon should not find himself having to recant because of unexpected technical difficulties. Similarly the option for the drainage procedure would be drawn when the field had been carefully inspected.

The institution of this trial has in no way influenced the selection of patients for surgery nor has it changed our policy of adapting the magnitude of the operation to the acid secretory status modified, on occasion, by considerations of age, sex, occupation, family history and general health of the patient.

/Thus

Thus patients with a "maximal" acid output of less than 30 m.eq./hr. have been treated by gastroenterostomy alone. Antrectomy has been added to vagotomy in some patients with M.A.O.'s of greater than 50 m.eq./hr. The author does not adhere to the latter policy on the grounds that antral resection is not only unnecessary in the presence of a satisfactory vagotomy but exposes the patient to an increased operative risk and later achlorhydria.

The survey began in May, 1968. Vagotomy has since been performed in 81 patients. These operations have been carried out by 12 surgeons. Six surgeons have performed only one operation each so that 75 (or 92% of the series) have been performed by six surgeons of whom three were consultants, one a senior registrar, and two were registrars.

Trial of Vagotomy

Table IV, 14 shows the proportion of patients admitted to the trial and the preferred operations for those not admitted. Consultants and junior staff are approximately equally represented. All patients undergoing vagotomy are included in the total. Of these, 45 (56%) were admitted to the trial. This at first sight would appear to be an unsatisfactory proportion, but a closer look at the case-material provides some explanation.

The reasons for exclusion are shown in Table IV, 15. Anatomical difficulties (seven cases) included a narrow subcostal angle, a large left lobe of liver and narrowing of the

/subdiaphragmatic

PEPTIC ULCER SURVEY AND THE ADMISSION OF PATIENTS
TO THE TRIAL.

OPTION I: TRUNCAL OR SELECTIVE VAGOTOMY

Surgeon	No. of Cases	Option Accepted	Operation preferred if option refused	
			Truncal	Selective
A	8	5	2	1
B	8	5	3	0
C	15	6	7	2
D	23	21	2	0
E	14	6	8	0
F	7	2	5	0
G - L	6	0	4	2
	81	45	31	5

A - C = Consultants
D - F = Junior Staff

G - L = Surgeons (Consultants or
Junior Staff) who only
performed one operation each.

TABLE IV, 14

REASONS GIVEN FOR WITHHOLDING PATIENTS
FROM TRIAL OF VAGOTOMY

<u>Technical</u>	
Anatomical difficulties	7
Surgeon's inexperience	5
Pathological difficulties	4
Re-vagotomy	4
Previous gastric surgery	3
	<hr/> 23
<u>Miscellaneous</u>	
Surgeon's preference (for S.V.)	3
Demonstration operation	3
Emergency	5
No reason given	2
	<hr/> 13

TABLE IV, 15

subdiaphragmatic space by a tortuous aorta. On five occasions junior staff listed "inexperience" of selective vagotomy as a reason for not drawing an option. Pathological difficulties (four cases) included obesity, the presence of adhesions and hiatus hernia. Selective vagotomy was not regarded as suitable in re-vagotomy operations (four cases). Previous gastric surgery other than vagotomy led to a preference for truncal vagotomy in three cases. Vagotomy was performed as a demonstration by or for visiting surgeons in three cases and five were emergency operations in which the patient was thought unfit for the more prolonged procedure. "Surgeon's preference" includes two cases where selective vagotomy was performed without drainage and one where the surgeon preferred selective vagotomy because the patient was a hospital employee.

If we exclude the latter group plus the patients who had previous gastric surgery and also the demonstration and emergency operations, we are left with 18 cases where technical reasons dictated the choice. 'Technical reasons' thus include anatomical and pathological obstacles and also the surgeon's inexperience. It will be observed that surgeons differed widely in their willingness to admit patients to the trial. Here the most telling factor was surgical experience. Closer supervision and tuition of junior staff could remedy this weakness.

/After

After excluding the categories listed above we find that in elective, "first-time" operations for duodenal ulcer 72% have been admitted to the trial. Considering the number of surgeons and their varied experience, this proportion is considered fairly satisfactory.

The Drainage Operation

The choice of drainage procedure is shown in Table IV, 16. The surgeon proved willing to draw an option in 36 cases. The reason for excluding nine cases was that operation other than drainage was proposed, either vagotomy with antrectomy or vagotomy alone. Reasons for exclusion in a further 11 cases included the presence of previous gastric operations (6), bleeding duodenal ulcer (4) and the presence of a prepyloric ulcer which required biopsy (1).

This in 20 cases a free choice of drainage procedure was not available for the surgeon. In the remaining 61 cases, 36 (59%) were admitted to the trial.

It will be observed that where an option was not drawn, cases were almost equally divided between gastroenterostomy and pyloroplasty. Table IV, 17 lists the reasons for refusal to draw an option. Reasons of technical difficulty comprise the majority.

Discussion

Surgeons acquiesced more often to a blind option on vagotomy than on the drainage operation. The comparison is not entirely a fair one since it is true to say the refusal to draw an option

/on

PEPTIC ULCER SURVEY AND THE ADMISSION OF PATIENTS
TO THE TRIAL.

OPTION II: GASTROENTEROSTOMY OR PYLOROPLASTY

Surgeon	No. of Cases	Option Accepted	Operation preferred if option not accepted		
			G.E.	Pyloro.	Other
A	8	3	1	3	1
B	8	4	1	1	2
C	15	6	3	2	4
D	23	15	5	3	0
E	14	4	4	1	1
F	7	2	2	3	0
G - L	6	2	1	2	1
	81	36	17	15	9

TABLE IV, 16

THE REASONS FOR WITHHOLDING PATIENTS FROM TRIAL OF DRAINAGE
PROCEDURE IN 23 CASES

(The patients are grouped according to the operation preferred by the surgeon).

Pyloroplasty

Surgeon's preference	7
Difficult mesocolon	2

Gastroenterostomy

Difficult duodenum	13
Surgeon's preference	<u>1</u>
	<u>23</u>

TABLE IV, 17

on the vagotomy, with three specified exceptions, was motivated by an unwillingness to attempt selective vagotomy. Refusal to take an option on the drainage was not due to a wish to avoid predominantly one of the choices, since gastroenterostomy and pyloroplasty were performed in approximately equal numbers in the withheld cases.

The author performs selective vagotomy as his operation of choice, whereas others taking part prefer truncal vagotomy. Such preferences naturally influence the proportion of patients included in the trial, but an admission rate of 72% suggests that from a technical viewpoint selective vagotomy can be recommended as a routine operation for duodenal ulcer. There is no operation that can be applied in every case.

A trial of vagotomy such as this cannot be successful without the very willing co-operation of all the surgical staff. Post-operative secretion studies are in progress and the clinical follow-up will be arranged with care in the hope of making a worthwhile contribution to our knowledge of the relative merits of these two operations.

C O N C L U S I O N S

Anatomy

1. Variations in the pattern of the abdominal vagus nerves are common. Their presence does not preclude successful selective vagotomy.
2. Particular study of this anatomy is essential for the surgeon wishing to achieve consistent complete gastric vagotomy. For selective vagotomy special attention must be paid to the varying patterns of the hepatic division of the anterior vagus and of the relationship of the posterior trunk and coeliac division to the left gastric artery. Common to both selective and truncal vagotomy is the need to study the variable nerve distribution around the lower oesophagus.
3. If truncal vagotomy is confined to the division of single anterior and posterior trunks the surgeon can expect an incidence of incomplete vagotomy exceeding 50%.
4. Emphasis upon these aspects of surgical anatomy is resulting in a lowered incidence of incomplete vagotomy in our unit, as demonstrated by insulin secretion tests.
5. A simplified method for selective vagotomy is described which avoids detailed dissection and which depends upon the isolation and division of neurovascular pedicles, thereby lending itself to the development of a standardised and reproducible technique.

Antrectomy and the neurohormonal mechanism of gastric secretion -

6. The vagal-release of gastrin and the synergism of the neural and humoral components gain further support from these studies in the dog and the human.

7. Operative antral mapping is described and the definition of 'antrum' in terms of gastrin-producing area is discussed.
8. Dog experiments show complete antrectomy to reduce vagus-stimulated acid secretion (but not pepsin) by approximately 60%. Should the surgeon fail to remove all the antrum a substantial reduction in vagus-stimulated secretion still occurs, but the mean reduction is less and is very variable.
9. Antrectomy in man has a similar effect on vagus-stimulated acid secretion. The implications for the interpretation of the insulin test of gastric secretion are discussed. The main points to be made here are that after 'antrectomy' a negative insulin test cannot be interpreted as indicating complete vagotomy and a positive test may indicate that both the antrectomy and the vagotomy are incomplete. Complete vagotomy with complete antrectomy is likely to result in achlorhydria.

The Insulin Secretion Test

10. This test, as generally performed and interpreted is very unsatisfactory. Consequently many reports concerning the incidence of incomplete vagotomy in the literature must be inaccurate; probably representing a serious underestimate.
11. Insulin exhibits both stimulatory and inhibitory effects upon gastric acid secretion, therefore the dose used in this test is critical. The evidence points to 0.15 units/kg. insulin being the optimal dose both in dog and in man.

12. The criteria other than those of Hollander by which the insulin test can be interpreted have been analysed in tests on 110 post-vagotomy patients, together with an analysis of the value of basal acid and M.A.O. measurements. The following paragraphs list the principal conclusions:-

13. Post-operative tests performed before the patient leaves hospital are unreliable.

14. Both basal acid and M.A.O. measurements, while providing excellent mean correlations with the insulin response show ranges which are too wide to allow these tests to be used as sole criteria.

15. The insulin test remains the single most effective test of completeness of vagotomy. It is recommended that the scoring system of Bank, Marks and Louw (1967) be used together with a record of the timing of the positive response.

16. On the basis of this series it is further suggested that it may be possible to estimate the per cent probability of a patient developing recurrent ulcer. A nomogram (Fig. III, 30) is provided as a model upon which further evaluation of this concept may be based.

17. The logical extension of this concept is the possibility of abolishing recurrent ulcer by selection of patients for elective prophylactic re-operation on the basis of post-operative secretion tests.

Incomplete/

Incomplete Vagotomy and Recurrent Ulcer -

18. If we performed better vagotomies the above concept would not be necessary. In the absence of an extravagal pathogenesis (e.g. suture-line ulcer; Zollinger-Ellison Syndrome) there is no satisfactory evidence that duodenal ulcer can recur, or jejunal ulcer occur, in the presence of complete gastric vagotomy.

19. Vagotomy has suffered in the past from being an operation that is too easy, or apparently so. Analysis of the results of insulin secretion tests in this series suggests that an applied interest in the vagal anatomy, a meticulous surgical technique and the closely supervised training of junior surgeons could minimise or even abolish recurrent ulcer as a clinical problem.

20. The completeness or otherwise of vagotomy has not influenced to any appreciable extent the incidence of other post-operative problems.

Selective Vagotomy

21. Selective vagotomy is not advocated for indiscriminate or universal application. In at least 75% of cases it is not a technically difficult operation.

22. The theoretical advantages of this operation are not yet established in practice. There are signs of a lessened incidence of severe diarrhoea. Controlled studies with an adequate duration of follow-up are not yet available.

23./

23. In their concluding remarks to the recent and most comprehensive review yet published of the results of vagotomy (Williams and Cox 1969) the editors give their view that -

"If the case for selective vagotomy were over-stated, we fear that its general adoption might become the cause of a high rate of incomplete gastric vagotomy".

The available evidence in the literature, supported by the data in this thesis, points to a directly contrary conclusion. Selective vagotomy results in an improved incidence of complete vagotomy. With the technique described in this thesis there is no reason why selective vagotomy, even if poorly executed, should be less effective than truncal vagotomy.

24. A better case could be made against selective vagotomy on the grounds that its indiscriminate use would probably give rise to an increased operative morbidity.

THE FUTURE

The star of vagotomy appears to be still in the ascendant. Yet we have seen that it carries many liabilities in its train. The ills of vagotomy are not always easy to separate from the ills of the accompanying procedure. By interfering with the mechanism of gastric emptying we produce bilious vomiting, dumping and possibly diarrhoea.

There/

There are two possible ways of avoiding destruction or by-pass of the pylorus. One is to perform sleeve-resection of the distal stomach, the other is to rely on vagotomy alone to reduce gastric acidity. The first takes us back to the perhaps unnecessary hazards of gastric resection and the unpredictable effects of residual antral tissue. The second carries both promise and reservations.

Several points suggest that vagotomy alone should be given a further trial. Firstly we are operating much earlier in the course of duodenal ulcer disease. The concept of the operation 'earned' by years of pain and disability is no longer valid. Thus it should be possible to avoid in a proportion of cases the chronic scarring and deformity of the pylorus and duodenum which must inevitably have contributed to the gastric stasis when vagotomy was formerly used as the sole procedure. Secondly in selective vagotomy we have a means of preserving the extrinsic nerve supply to pylorus and duodenum. The possible advantages of this in terms of motility and gastric emptying have yet to be fully investigated. Thirdly there are tests of gastric emptying which should allow us to select patients appropriate for such an operation.

Reservations concern the surgeon's ability consistently to achieve the necessary complete gastric vagotomy. The author believes that with sufficiently careful technique this can be done, even in the absence of a satisfactory per-operative test of vagotomy.

In/

In the field of clinical research important needs highlighted by these studies include the performance of insulin dose-response studies in patients showing 'weak-positive' or 'borderline' responses; further evaluation of post-vagotomy secretory data to detect those patients at risk of developing recurrent ulcer; the search for tests to demonstrate the function of non-gastric vagal branches and the continuation of controlled trials of selective versus truncal vagotomy with adequate long-term follow-up and post-operative secretion tests. It is intended that the studies described in this thesis will be extended in pursuit of these goals.

REFERENCES .

REFERENCES

- Amdrup, E., Clemmesen, T. and Andreassen, J. (1966).
"Selektiv Vagotomi". Nordisk Medicin 13 X, 76: 1180.
- Anderson, H. A. (1966). "Postvagotomy Dysphagia".
Gastroint: Endosc. 12: 13.
- Aylett, P. (1962). "The Effects of Glucagon and Glucagon-Free
Insulin upon Gastric Secretion in Peptic Ulcer Patients".
Clin. Sci. 22: 179.
- Babkin, B. P. (1934). "The Chemical Phase of Gastric Secretion
and its Regulation". Am. J. Dig. Dis. 1: 715.
- Bachrach, W. H. (1962). "Laboratory Criteria for the
Completeness of Vagotomy". Am. J. Dig. Dis. N.S. 7: 1071.
- Bachrach, W. H. (1963). "On the Question of a Pituitary-Adrenal
Component in the Gastric Secretory Response to Insulin
Hypoglycaemia". Gastroenterology, 44: 178.
- Ballinger, W. F. (1963). "The Small Intestine following Vagotomy".
Surg. Gynae. Obst. 116: 115.
- Ballinger, W. F., Iida, J., Aponte, G. E., Wirts, C. W. and
Goldstein, F. (1964). "Structure and Function of the
Canine Small Intestine following Total Abdominal Vagotomy".
Surg. Gynae. Obst. 118: 1305.
- Ballinger, W. F., Padula, R. T. and Camishon, R. C. (1965).
"Mesenteric Blood Flow following Total and Selective
Vagotomy". Surgery, 57: 409.
- Bank, S., Marks, I. N. and Louw, J. H. (1967). "Histamine and
Insulin-stimulated Gastric Acid Secretion after Selective
and Truncal Vagotomy. Gut, 8: 36.
- Barnes, A. D. and Cox, A. G. (1969). "Diarrhoea" - In 'After
Vagotomy' (Ed. J. Williams and A. G. Cox) Butterworths,
London, Ch. 17 p. 211.
- Barnes, A. D. and Williams, J. A. (1967). "The Change of Bowel
Habits following Vagotomy and Pyloroplasty". Brit. J. Surg.
54: 218.

Bartholinus/

- Bartholinus, T. (1651). "Anatomia". Lugd. Bat. Hackium, Leyden, Ch. 9.
- Bastable, J. R. G. (1965). "Vagotomy and Pancreatic Function". Brit. J. Surg. 52: 459.
- Bell, P. R. (1963). "Communication to Postgraduate Course in Gastroenterology" - Glasgow.
- Bensley, R. R. (1899). "The Structure of the Mammalian Gastric Glands". Quart. J. Micro. Sci. 41: 361.
- Bergström, H. and Broome, A. (1964). "Peroperative Determination of the Boundary between the Gastric Antrum and Fundus". Acta. Chir. Scand. 128: 526.
- Bourguery, J. M. (1839). "Traite Complet de L'Anatomie de l'Homme". Ed. Delaunay, Jules Didot L'Aine, Paris, Vol. V.
- Bradley, W. F., Small, J. T., Wilson, J. W. and Walters, W. (1947). "Anatomic Considerations of Gastric Neurectomy". J.A.M.A. 133: 459.
- Brooks, F. P. and Manfredo, H. (1964). "The Control of Pancreatic Secretion and its Clinical Significance. Am. J. Gastroent. 42: 42.
- Bruce, J., Card, W. I., Marks, I. N. and Sircus, W. (1959). "The Rationale of Selective Surgery in the Treatment of Duodenal Ulcer". J. Roy. Coll. Surg. Ed. 4: 85.
- Bruce, J. and Small, W. P. (1959). "Dysphagia following Vagotomy". J. Roy. Coll. Surg. Ed. 4: 170.
- Bryant, W. M., Klein, D. and Griffen, W. O. (1967). "The Role of Vagotomy in Duodenal Ulcer Surgery". Surgery, St. Louis, 61: 864.
- Bulbring, E. (1961). "Motility of the Intestine". Proc. Roy. Soc. Med. 54: 773.
- Bulbring, E. and Gershon, M. D. (1968). "Serotonin Participation in the Vagal Inhibitory Pathway to the Stomach". Advances Pharmacol. 6A: 323.
- Burge/

Burge, H. (1961). "The Hepatic Vagal Plexus". *Lancet*, ii: 899.

Burge, H. and Vane, J. R. (1958). "Method of Testing for Complete Nerve Section during Vagotomy". *Brit. Med. J.* 1: 615.

Burge, H. (1964). "Vagotomy". Edward Arnold, London.

Burge, H. (1968). Personal Communication.

Burge, H., Rizk, A. R., Tompkin, A. M. B., Barth, C. E., Hutchison, J. S. F., Longland, C. J., McLennan, I. and Miln, D. C. (1961). "Selective Vagotomy in the Prevention of Post-Vagotomy Diarrhoea". *Lancet*, ii: 897.

Burge, H. and Pick, E. J. (1958). "Long-term Results of Vagotomy and Gastroenterostomy on Chronic Duodenal Ulcer." *Brit. Med. J.* 1: 613.

Burnett, W., Cairns, F. W. and Bacsich, P. (1964). "Some Observations on the Innervation of the Extrahepatic Biliary System in Man". *Ann. Surg.* 159: 8.

Butler, T. J. (1960). "A Study of Pancreatic Response to Food after Gastrectomy in Man." *Gut*, 1: 55.

Butler, T. J. and Eastham, R. D. (1965). "Absorption Studies after Gastrojejunostomy with and without Vagotomy". *Gut*, 6: 69.

Cammock, E. E., Nyhus, L. M. and Harkins, H. N. (1963). "The Study of the Biphasic Curve of Gastric Secretion following Insulin Stimulation". *Am. J. Dig. Dis.* 8: 337.

Capper, W. M., Laidlaw, C. D. A., Buckler, K. and Richards, D. (1963). "The pH Fields of the Gastric Mucosa". *Lancet*, 2: 1200.

Capper, W. M., Butler, T. J., Buckler, K. G. and Hallett, C. P. (1966). "Variation in Size of the Gastric Antrum". *Ann. Surg.* 163: 281.

Card, W. I. and Marks, I. N. (1960). "The Relationship between the Acid Output of the Stomach following 'Maximal' Histamine Stimulation and the Parietal Cell Mass". *Clin. Sci.* 19: 147.

Casten/

- Casten, D. F., Larkin, A. and Quiroga, F. G. (1967).
 "Treatment of Duodenal Ulcer in a Small Metropolitan
 Community Hospital". *Am. J. Surg.* 113: 335.
- Celestin, L. R. (1967). "Gastrin-like effects of Cholecystokinin-
 Pancreozymin". *Nature*, 215: 763.
- Chamberlain, J. A. and Winship, T. (1947). "Anatomic Variations
 of the Vagus Nerves - Their Significance in Gastric
 Neurectomy". *Surgery*, 22: 1.
- Checketts, R. G., Gillespie, I. E. and Kay, A. W. (1966).
 "Propantheline as an Agent for Medical Vagotomy".
Gut, 7: 200.
- Cheselden, W. (1795). "The Anatomy of the Human Body".
 Manning and Loring, Boston, Chapter XV, p. 238.
- Clark, C. G., Murray, J. G., Slessor, I. M. and Wyllie, J. H.
 (1964). "Complete Vagotomy and its Consequences:
 Follow-up of 146 Patients. *Brit. Med. J.* 2: 900.
- Cloquet, J. (1828). "Anatomie De L'Homme". Engelmann, Paris,
 Vol. III.
- Cole, F. J. (1944). "A History of Comparative Anatomy".
 MacMillan, London, p. 45.
- Collins, E. N., Crile, G. and Davis, J. B. (1948). "Follow-up
 of Vagotomy plus Gastroenterostomy or Pyloroplasty for Ulcer".
Gastroenterology, 11: 453.
- Cox, A. G. (1969). "The Pancreas" in - "After Vagotomy"
 Ed. J. A. Williams and A. G. Cox, Butterworth, London,
 Ch. 5.
- Cox, H. T., Coherty, J. F. and Kerr, D. F. (1958). "Changes in
 the Gall-bladder after Elective Gastric Surgery".
Lancet, i: 764.
- Cox, A. G. and Bond, M. R. (1964). "Bowel Habit after Vagotomy
 and Gastrojejunostomy". *Brit. Med. J.* 1: 460..
- Cox, A. G., Bond, M. R., Podmore, D. A. and Rose, D. P. (1964).
 "Aspects of Nutrition after Vagotomy and Gastrojejunostomy".
Brit. Med. J. i: 465.

Craft/

- Craft, I. L. and Venables, C. W. (1968). "Antiperistaltic segment of Jejunum for Persistent Diarrhoea following Vagotomy". *Ann. Surg.* 167: 282.
- Crooke, H. (1631). "Microcosmographia. A Description of the Body of Man. Together with the Controversies thereto Belonging". 2nd Ed.: Thos. and Richard Cotes, London.
- Davis, R. A. and Brooks, F. B. (1962). "Variability of Gastric Secretory Response to Insulin Hypoglycaemia". *Gastroenterology* 44: 178.
- Dellipiani, A. W. and Girdwood, R. H. (1967). "The Significance of Abnormal Bacterial Proliferation in the Gastro-intestinal Tract after Gastric Surgery". *Scand. J. Gastroent.* 2: 161.
- Dragstedt, L. R. (1946). "Section of the Vagus Nerves to the Stomach". *Surg. Gynae. and Obst.* 83: 547.
- Dragstedt, L. R., Harper, P. V., Tovee, E. B. and Woodward, E. R., (1947). "Section of Vagus Nerves to the Stomach in the Treatment of Peptic Ulcer: Complications and End-results after four years". *Ann. Surg.* 126: 687.
- Dreiling, D. A. and Janowitz, H. D. (1959). "The Effect of Glucagon on Gastric Secretion in Man". *Gastroenterology*, 36: 580.
- Dreiling, D. A., Druckermann, L. J. and Hollander, F. (1952). "The Effect of Complete Vagisectomy and Vagal Stimulation on Pancreatic Secretion in Man". *Gastroenterology*, 20: 578.
- Duke, W. W., Hirschowitz, B. I. and Sachs, G. (1965). "Vagal Stimulation of Gastric Secretion by 2 Deoxy-D-Glucose". *Lancet* ii: 871.
- Duthie, H. L. (1965). "Intestine" - In - 'The Scientific Basis of Surgery'. Ed. W. I. Irvine, Churchill, London, Ch. 4, p. 58.
- Duthie, H. L. (1969). "Pre-operative Acid Tests" - In - 'After Vagotomy'. Ed. J. A. Williams and A. G. Cox, Butterworth, London, Ch. 18.
- Edkins, J. S. (1906). "The Chemical Mechanism of Gastric Secretion". *J. Physiol.* 34: 183.
- Eisenberg, M. N., Woodward, E. R., Quintana, R. and Dragstedt, L. R. (1963). "Insulin Inhibition of Gastric Secretion". *J. Surg. Research* 3: 479.

- Elliot, R. L., Barnett, W. O. and Elliot, M. C. (1967).
"An Ultrastructural Study of the Small Intestine after
Vagotomy". Surg. Gynae. and Obst. 124: 1037.
- Ellis, H. and Pryse-Davies, J. (1967). "Vagotomy in the Rat;
A Study of its Effects on Stomach and Small Intestine".
Brit. J. Exp. Path. 48: 135.
- Evans, D. H. L. and Murray, J. G. (1954). "Histological and
Functional Studies on the Fibre Composition of the Vagus
Nerve of the Rabbit". J. Anat. 88: 320.
- Evans, R. H., Zajtchuk, R. and Menguy, R. (1967). "Role of
Vagotomy and Gastric Drainage in the Surgical Treatment of
Duodenal Ulcer". Surg. Clin. N. Amer. 47: 141.
- Farris, J. M. and Smith, G. K. (1963). "Vagotomy and Pyloroplasty
for Bleeding Duodenal Ulcer". Am. J. Surg. 105: 388.
- Fields, M. and Duthie, H. L. (1965). "Effects of Vagotomy on
Intraluminal Digestion of Fat in Man". Gut, 6: 30.
- Fox, H. J. and Grimson, K. S. (1950). "Defective Fat Absorption
Following Vagotomy". J. Lab. Clin. Med. 35: 362.
- Frankson, G. A. (1948). "Selective Gastric Vagotomy".
Acta. Chir. Scand. 96: 409.
- French, J. D., Longmire, R. L., Porter, R. W. and Marius, H. J.
(1953). "Extravagal Influences on Gastric Hydrochloric
Acid Secretion Induced by Stress Stimuli". Surgery, 34: 621.
- Freston, J. W. and Bouchier, I. A. D. (1968). "The Influence of
Total Vagotomy on Dihydrocholesterol-Induced Cholelithiasis
in Rabbits". Gastroenterology, 54: 153.
- Forrest, A. M. and Code, C. F. (1954). "Effect of Sympathectomy
and Vagotomy on the Inhibition by Insulin of Histamine-
Induced Secretion in Separated (Heidenhain) Canine Pouches".
Am. J. Physiol. 177: 430.
- Frohn, M. J., Desai, S. and Burge, H. (1968). "Bilateral
Selective Vagotomy in Prevention of Post-Vagotomy Diarrhoea".
Brit. Med. J. 1: 481.
- Fyffe, A. (1830). "Ond Hundred and Fifty Eight Plates to
Illustrate the Anatomy of the Human Body". Adam Black,
Edinburgh. Legend to Tab. CLIV.

Gillespie/

- Gillespie, I. E., Clark, D. H., Kay, A. W. and Tankel, H. I. (1960) "Effect of Antrectomy, Vagotomy with Gastro-jejunostomy, and Antrectomy with Vagotomy on the Spontaneous and Maximal Gastric Acid Output in Man." *Gastroenterology*. 38: 361.
- Gillespie, I. E. and Kay A. W. (1961). "Effect of Medical and Surgical Vagotomy on the Augmented Histamine Test in Man." *Br. Med. J.* 1: 1557.
- Gillespie, G., Gillespie, I. E. and Kay, A. W. (1968). "An Analysis of the Insulin Test after Vagotomy using Single and Multiple Criteria". *Gut*. 9: 470.
- Glanville, J. N. and Duthie, H. L. (1964). "Contraction of the Gall-Bladder Before and After Total Abdominal Vagotomy". *Clinical. Radiology*, 15: 350.
- Glass, G. B. J. and Wolff, S. (1950). "Hormonal Mechanisms in Nervous Mechanisms of Gastric Acid Secretion in Humans". *Proc. Soc. Expl. Bio. Med.* 73: 535.
- Goligher and Others (1968). "Five-to-Eight year Results of Leeds/York Controlled Trial of Elective Surgery for Duodenal Ulcer." *Brit. Med. J.* 2: 781.
- Goligher, J. C. and Pulvertaft, C.N. (1969). "Comparison of Different Operations" in "After Vagotomy". Eds. J. A. Williams and A. G. Cox. Butterworths, London. Ch. 8: 93.
- Govaerts, J. P. and Kiekens, R. (1968). "Role of Vagal Innervation on Pancreatic Secretion". *Surgery*, 63: 942.
- Gregory, R. A. (1968). "Memorial Lecture. The Isolation and Chemistry of Gastrin". *Gastroenterology*, 54: 723.
- Gregory, R. A. and Ivy, A.C. (1941). "Humoral Stimulation of Gastric Secretion". *Quart. J. Exptl. Physiol.* 31: 111.
- Gregory, R. A. and Tracey, H. J. (1960). "The Constitution and Properties of Two Gastrins Extracted from Hog Antral Mucosa." *Gut*. 5: 1031.
- Griffiths, C. A. (1960). "Gastric Vagotomy vs Total Abdominal Vagotomy." *Arch. Surg.* 81: 781.
- Griffiths, C. A. (1962). "Selective Gastric Vagotomy" in "Surgery of the Stomach and Duodenum." Ed. Harkins and Nyhus, Little, Brown & Co., Boston, 10B7; 505.

/Griffiths

- Griffiths, C. A. and Harkins, H. N. (1957). "Partial Gastric Vagotomy. An Experimental Study". *Gastroenterology*, 32: 971.
- Griffiths, C. A., Stavney, L. S., Kato, T. and Harkins, H. N. (1963). "Selective Gastric Vagotomy". *Am. J. Surg.* 105: 13.
- Griffiths, J. M. T., and Holmes, G. (1964). "Cholecystitis following Gastric Surgery." *Lancet*, 2: 780.
- Grossman, M. I. (1966). "Measurement of Gastric Acidity". *Lancet* 2: 1312.
- Grossman, M. I. and Marks, I. N. (1960). "Secretion of Pepsinogen by the Pyloric Glands of the Dog, with some Observations on the Histology of the Gastric Mucosa." *Gastroenterology*, 38: 343.
- Harper, A. A., Kidd, C. O. and Scratcherd, T. (1959). "Vago-vagal Reflex Effects on Gastric and Pancreatic Secretion and Gastrointestinal Motility." *J. Physiol.* 148: 417.
- Harris, J. and Miller, C. M. (1960). "Cardiospasm following Vagotomy." *Surgery* 47: 568.
- Harrison, R. C., Lakey, W. H. and Hyde, H. A. (1956). "Production of Acid Inhibition by Gastric Antrum." *Ann. Surg.* 144: 441.
- Harrison, R. C., Williams, H. T. G., Pisesky, W., Husain, S., Silbermann, O. H., Francis, G. J. and Irvine, J. W. (1961). "The Relative Importance of the Vagus Nerve, antrum and acid-secreting Mucosa in the Prevention of Experimental Peptic Ulceration." *Surgery*, 50; 151.
- Hedensted, S. and Lundquist, G. (1966). "Selective Gastric Vagotomy versus Total Abdominal Vagotomy." *Acta. Chir. Scand.* 131: 448.
- Heydn, S. (1956). "Kungl. Lantbrukshogskolans." *Annaler.* 22: 139.
- Hilbrun, G. R. and Barnett, W. O. (1965). "Dissolution of Human Gall-stones in the Dog's Gall-Bladder after Various Degrees of Vagotomy." *Surg. Forum* 16: 390.
- Hirschowitz, B.I. and O'Leary, D. K. (1964). "Dose Dependence of Insulin Stimulated Gastric Secretion." *Am. J. Dig. Dis.* 9: 379.

Hirschowitz/

- Hirschowitz, B. I. and Sachs, G. (1965). "Vagal Gastric Secretory Stimulation by 2 Deoxy-D-Glucose". *Am. J. Physiol.* 209: 452.
- Hoffman, H. H. and Schnitzlein, H. N. (1961). "The Numbers of Nerve Fibres in the Vagus Nerve of Man". *Anat. Rec.* 139: 429.
- Hollander, F. (1946). "The Insulin Test for the Presence of Intact Nerve Fibres after Vagal Operations for Peptic Ulcer". *Gastroenterology*, 7: 607.
- Hollander, F. (1948). "Laboratory Procedures in the Study of Vagotomy with Particular Reference to the Insulin Test". *Gastroenterology*, 11: 419.
- Holmquist, B. and Colleen, S. (1965). "Secretion of Pancreatic Juice following Vagotomy". *Acta. Chir. Scand.* 130: 111.
- Hoveacque, A. (1927). "Anatomie des Nerfs Craniens et Rachidiens et du Systeme Grand Sympathique Chez l'homme". Ch. 2, p. 206. Gaston Doin et Cie, Paris.
- Hubel, K. A. (1964). "Insulin-Induced Gastric Secretion: Reproducibility of Results". *Clin. Res.* 12: 341.
- Hunt, J. N. (1950). "An Interpretation of Histamine and Insulin Tests in Patients with Peptic Ulceration". *Lancet*, 2: 397.
- Hyde, G. L. and Hull, D. A. (1965). "Selective Gastric Vagotomy". *Southern Med. J.* 58: 740.
- Iggo, A. and Leek, B. F. (1967). "An Electrophysiological Study of Single Vagal Efferent Units Associated with Gastric Movements in Sheep". *J. Physiol.* 191: 177.
- Isaac, F., Ottoman, R. E. and Weinberg, J. A. (1950). "Roentgen Studies of the Upper Gastro-Intestinal Tract in Vagotomy". *Am. J. Roent.* 63: 66.
- Jackson, R. G. (1948). "Anatomic Study of the Vagus Nerves". *Arch. Surg.* 57: 333.
- Jacobson, E. D. (1965). "The Circulation of the Stomach". *Gastroenterology*, 48: 85.
- Janowitz/

- Janowitz, H. D. and Hollander, F. (1951). "Critical Evidence that the Vagus does not release Gastrin." Proc. Soc. Exp. Biol. Med. 76: 49.
- Jepson, K. and Johnston, D. (1968). "Effect of Vagotomy on Human Gastric Acid Secretion Stimulated by Gastrin Pentapeptide and by Histalog." Gastroenterology, 55: 665.
- Johnson, F. E. and Boyden, E. A. (1952). "The Effect of Sectioning Various Autonomic Nerves upon the Rate of Emptying of the Biliary Tract in the Cat." Surg. Gynec. and Obst. 76: 395.
- Johnston, D., Goligher, J. C. and Duthie, H. L. (1966). "Medical Vagotomy: An Assessment." Br. Med. J. 2: 1481.
- Johnston, D., Thomas, D. G., Checketts, R. G. and Duthie, H. L. (1967). "An Assessment of Post-Operative Testing for Completeness of Vagotomy." Br. J. Surg. 54: 831.
- "
- Jordan, P. H. and Sand, B. F. (1957). "Antral Inhibition of Gastric Secretion." Proc. Soc. Exp. Biol. Med. 94: 471.
- Kay, A. W. (1967). "Memorial Lecture: An Evaluation of Gastric Acid Secretion Tests." Gastroenterology. 53: 834.
- Kay, A. W. (1953). "Effect of Large Doses of Histamine on Gastric Secretion of HCl." Brit. Med. J. 2: 77.
- Kay, A. W. (1969). "Introduction" in 'After Vagotomy'. Eds. J. A. Williams and A. G. Cox. Butterworths, London Ch. 1. p. 1.
- Keen, J. A. (1966). "A Note on the Fibre Composition of the Vagus Nerves in Man." S. Afr. Med. J. 40, 981.
- Kemp, D. R., Herrera, F., Tsukamoto, M., and Eisenberg, M. M. (1968). "Insulin-Potassium Effect on Gastric Acid Secretion and Antral Motility in Dogs." Gastroenterology 54: 190.
- Kennedy, T. and Connell, A. M. (1969). "A Double-Blind Controlled Trial of the Value of Selective and Total Vagotomy in the Surgical Treatment of Duodenal Ulcer." Brit. J. Surg. 56: 385.
- Klotz, A. P. and Duvall, M. R. (1957). "The Laboratory Determination of Pepsin in Gastric Juice with Radioactive Iodinated Albumin." J. Lab. Clin. Med. 50: 753.

Kemarov/

- Komarov, S. A. and Marks, I. N. (1958). "Esophagostomy in the Dog Allowing Natural Feeding." *Proc. Soc. Exp. Biol. Med.* 97: 574.
- Kraft, R. O., Fry, W. J. and Ransom, H. H. (1962). "Selective Gastric Vagotomy." *Arch. Surg.* 85: 687.
- Kraft, R. O. and Fry, W. J. (1963). "Operative Technique of Selective Gastric Vagotomy." *Amer. J. Surg.* 105: 423.
- Krawiec, J., Straughn, J. and Polish, E. (1965). "The Biphasic Gastric Secretory Response in Man." *Am. J. Dig. Dis.* 10: 985.
- Kuntz, A., (1946). "The Autonomic Nervous System." 3rd Ed. Ch. 10: 216.
- Kyle, J. and Stephens, F. (1951). "Gastric Acidity after Duodenal Ulcer Surgery." *Brit. J. Surg.* 48: 465.
- Lai, K. S. (1964). "Studies on Gastric." *Gut.* 5: 3271.
- Latarjet, M. M. (1922). "Résection des Nerfs de l'Estomac Technique Opératoire. Resultats Cliniques." *Bull. Acad. Med.* 87: 681.
- Legros, C. and Griffiths, C. A. (1968). "The Anatomic Basis for the Variable Adequacy of Incomplete Vagotomy." *Ann. Surg.* 168: 1030.
- Lenninger, S. G., Magee, D. F. and White, I. T. (1965). "Effect of Gastric, Extragastric and Truncal Vagotomy on the External Secretion of the Pancreas in the Dog." *Ann. Surg.* 162: 1057.
- Leonsins, A. J. and Waddell, W. R. (1958). "Inhibiting Effect of Norpinephrenic on Gastric Secretion in Human Subjects." *J. Appl. Physiol.* 12: 334.
- Lewis, E. B. (1938). "Acidity of Gastric Contents After Excision of the Antral Mucosa." *Surgery* 4: 692.
- Linde, S. (1954). "The Role Played by the Pyloric Region in the Cephalic Phase of Gastric Secretion." *Acta. Phys. Scand.* 32: 238.
- Lizars, J. (1856). "A System of Anatomical Plates of the Human Body." W. H. Lizars, Edinburgh.

Logan/

- Logan, H. (1964). "Steatorrhoea and Diarrhoea after Vagotomy: A Comparison of Drainage Procedures". *Gut*, 5: 88.
- Lubran, M. (1966). "Measurement of Gastric Acidity". *Lancet*, 2: 1070.
- Lynwood-Herrington (1967). "Vagotomy - Pyloroplasty for Duodenal Ulcer: A Critical Appraisal of Early Results". *Surgery*, 61: 698.
- Lythgoe, J. P. (1961). "Comparison of the Insulin and Electrical Stimulation Tests for Completeness of Vagotomy". *Brit. Med. J.* 1: 1196.
- McCann, J. (1929). "Studies on the Control of the Acidity of Gastric Juice". *Am. J. Physiol.* 89: 483.
- McCrea, E. D'A. (1929). "The Nerves of the Stomach and their Relation to Surgery". *Brit. J. Surg.* 13: 621.
- MacDonald, J. A. and Welsh, W. K. (1965). "The Immediate Results of Operations for Duodenal Ulcer". *Canad. Med. Ass. J.* 92: 652.
- McGuigan, J. E. (1968). "Gastric Mucosal Intracellular Localisation of Gastrin by Immunofluorescence". *Gastroenterology*, 55: 315.
- McKibben, B. and Naylor, F. D. (1962). "A Test for the Completeness of Vagotomy". *Brit. J. Surg.* 50: 92.
- Maddrey, W. C., Serebro, H. A., Marcus, H. and Iber, F. L. (1967). "Recovery, Reproducibility and Usefulness of Polyethylene Glycol, Iodine-labelled Rose Bengal, Sulphobromophthalein, and Indocyanine Green as Non-absorbable Markers". *Gut*, 8: 169.
- Madsen, P. and Pedersen, G. (1968). "Post-vagotomy Diarrhoea Examined by Means of a Nutritional Contrast medium". *Scand. J. Gastroent.* 3: 545.
- Malawer, S. J. and Powell, D. W. (1967). "An Improved Turbidimetric Analysis of Polyethylene Glycol Utilising an Emulsifier". *Gastroenterology*, 53: 250.
- Marshall, R. (1964). "Assessment of Post-operative Bowel Behaviour". *J. Roy. Coll. Surg. Edin.* p. 307.
- Mason/

- Mason, M. C., Giles, G. R., Graham, N. G., Clark, C. G. and Goligher, J. C. (1968). "An Early Assessment of Selective and Total Vagotomy". *Brit. J. Surg.* 55: 677.
- Melrose, A. G. (1960). "Effect of Glucagon on Gastric Secretion in Man". *Gut*, 1: 142.
- Middleton, M. D., Kelly, K. A., Nyhus, L. M. and Harkins, H. N. (1965). "Selective Vagal Effects on the Intestinal Phase of Gastric Secretion." *Gut*, 6: 296.
- Miller, E. M. and Davies, C. B. (1947). "An Anatomic Study of the Vagus Nerves". *J.A.M.A.* 133: 461.
- Mitchell, G. A. (1940). "A Macroscopic Study of the Nerve Supply of the Stomach". *Jour. Anat.* 75: 50.
- Moe, R. E., Klopfer, P. J. and Nyhus, L. M. (1965). "Demonstration of the Functional Anatomy of the Gastric Antrum". *Am. J. Surg.* 110: 277.
- Moore, F. D. (1948). "Follow-up of Vagotomy in Duodenal Ulcer". *Gastroenterology*, 11: 442.
- Moore, E. W. (1968). "Determination of pH by the Glass Electrode: pH Meter Calibration for Gastric Analysis". *Gastroenterology*, 54: 501.
- Moore, E. W. and Scarlata, R. W. (1965). "The Determination of Gastric Acidity by the Glass Electrode". *Gastroenterology*, 49: 178.
- Multicentre Study: "Intramuscular Pentagastrin Compared with other Stimuli as Tests of Gastric Secretion". *Lancet*, 1: 341, 1969.
- Mutt, V. and Jorpes, J. E. (1967). "Isolation of Aspartyl-Phenylalanine Amide from Cholecystokinin-Pancreozymin". *Biochem. Biophys. Res. Com.* 26: 392.
- Neilson, J. R. (1964). "The Development of Cholelithiasis following Vagotomy". *Am. J. Dig. Dis.* 9: 506.
- Nobles, E. R. (1966). "Vagotomy and Gastroenterostomy: 15-year Follow-up of 175 Patients". *Amer. Surg.* 32: 177.
- Oberhelman/

- Nyhus, L. M., Chapman, N. D., De Vito, R. V. and Harkins, H. N. (1960). "The Control of Gastrin Release: An Experimental Study Illustrating a New Concept". *Gastroenterology*, 39: 582.
- Oberhelman, H. A., Woodward, E. R., Zubiran, J. M. and Dragstedt, L. R. (1952). "Physiology of the Gastric Antrum". *Am. J. Physiol.* 169: 738.
- Ohio Chapter, American College of Surgeons (1967). "Elective Operations Performed for Duodenal Ulcer, with their Mortality". *Amer. J. Surg.* 114: 427.
- Oi, M., Oshida, K. and Sugimura, S. (1959). "The Location of Gastric Ulcer". *Gastroenterology*, 36: 45.
- Olbe, L. (1964). "Potentiation of Sham Feeding Response in Pavlov Pouch Dogs by Subthreshold Amounts of Gastrin with and without Acidification of Denervated Antrum". *Acta Physiol. Scand.* 61: 1.
- Olson, W. H. and Necheles, H. (1955). "Primary Depression of Gastric Secretion by Insulin in Normal Man". *J.A.M.A.* 159: 1013.
- Osborne, M. P. and Frederick, P. L. (1965). "A Simple Method for Precise Resection of the Gastric Antrum". *Surg. Gynae. Obst.* 121: 592.
- Palumbo, L. T. and Sharp, W. S. (1965). "Distal Antrectomy with Vagotomy". *Arch. Surg.* 91: 684.
- Palumbo, L. T., Paul, R. E. and Westly, G. T. (1952). "Partial Gastrectomy with and without Vagus Resection in the Treatment of Duodenal Ulcer". *Arch. Surg.* 64: 756.
- Passaro, E. and Grossman, M. I. (1964). "Effect of Vagal Innervation on Acid and Pepsin Response to Histamine and Gastrin". *Am. J. Physiol.* 206: 1068.
- Patterson, H. C. (1965). "Morbidity Following Gastric Resection for Duodenal Ulcer with and without Vagotomy". *Amer. Surg.* 31: 175.
- Payne, R. A. and Kay, A. W. (1962). "The Effect of Vagotomy on the Maximal Acid Secretory Response to Histamine in Man". *Clin. Sci.* 22: 373.

Pearson/

- Pearson, F. G., Stone, R. M., Parrish, R. M., Falk, R. F. and Drucker, W. R. (1969). "Role of Vagotomy and Pyloroplasty in the Therapy of Symptomatic Hiatus Hernia". *Am. J. Surg.* 117: 130.
- Pfeffer, R. B., Stephenson, H. E. and Hinton, J. W. (1952). "The Effect of Thoracolumbar Sympathectomy and Vagus Resection on Pancreatic Function in Man". *Ann. Surg.* 136: 585.
- Pollock, A. V. (1952). "Vagotomy in the Treatment of Peptic Ulceration". *Lancet*, 2: 795.
- Portal, A. (1804). "Cours D'Anatomie Medicale on Elemens de l'Anatomie de L'Homme". Baudouin, Paris, Vol. 4.
- Preshaw, R. M., Cooke, A. R. and Grossman, M. I. (1965). "Pancreatic Secretion induced by Stimulation of the Pyloric Gland Area of the Stomach". *Science*, 148: 1347.
- Pritchard, G. R., Griffiths, C. A. and Harkins, H. N. (1968). "A Physiologic Demonstration of the Anatomic Distribution of the Vagal System to the Stomach". *Surg. Gynae. Obst.* 1261: 791.
- Pritchard, G. R., Griffiths, C. A. and Harkins, H. N. (1968). "Visual Demonstration of the Vagal Release of Gastrin". *Amer. J. Surg.* 115: 191.
- Rendall, M. and Silen, W. (1969). "The Biliary Tract" - In - 'After Vagotomy' Eds. J. H. Williams and A. G. Cox, Butterworths, London, Ch. 4, p. 49.
- Richardson, K. C. (1960). "Studies on the Structure of Autonomic Nerves of the Small Intestine". *J. Anat.* 94: 457.
- Ritchie, W. P., Delaney, J. P., Barzilai, A., Molina, E., and Wangenstein, O. H. (1966). "Histological Differences between Heidenhain Pouches and their Parent Stomachs". *Surgery*, 60: 1224.
- Roholm, K. (1930). "Clinical Investigations with the Effect of Intravenous Injection of Insulin. IX. Gastric Secretion in Normal Individuals". *Acta Med. Scand.* 73: 472.
- Ross/

- Ross, B. and Kay, A. W. (1964). "The Insulin Test After Vagotomy". *Gastroenterology*, 46: 379.
- Ross, B., Watson, B. W. and Kay, A. W. (1963). "Studies on the Effect of Vagotomy on Small Intestinal Motility Using the Radio-Telemetering Capsule". *Gut*, 4: 77.
- Roth, H. P. and Beams, A. J. (1959). "The Effect of Vagotomy on the Motility of the Small Intestine". *Gastroenterology*, 36: 452.
- Ruckley, C. V. (1964). "A Study of the Variations of the Abdominal Vagi". *Brit. J. Surg.* 51: 569.
- Ruding, R. and Hurdes, W. H. (1953). "The Extent of the Gastric Antrum and its Significance". *Surgery*, 53: 743.
- Sauer, M. E. and Rumble, C. T. (1946). "The Number of Nerve Cells in the Myenteric and Submucous Plexus of the Small Intestine of the Cat". *Anat. Rec.* 96: 373.
- Sawyers, J. L., Scott, H. W., Edwards, W. H., Shull, H. J. and Law, D. H. (1968). "Comparative Studies of the Clinical Effects of Truncal and Selective Gastric Vagotomy". *Am. J. Surg.* 115: 165.
- Scarpa, A. (1831). "Tabulae Neurologicae". Trans R. Knox. MacLachlan and Stewart, Edinburgh.
- Schedl, H. P. (1966). "Use of Polyethylene Glycol and Phenol Red as Unabsorbed Indicators for Intestinal Absorption Studies in Man". *Gut*, 7: 159.
- Schein, C. J., Beneventano, T. C., Rosen, R. G., Dardik, H. M. and Gliedman, M. L. (1968). "Hepatic Plexus Vagotomy as an Adjunct to Cholecystectomy". *Surg. Gynae. Obst.* 128: 241.
- Schlicke, C. P. (1963). "Complications of Vagotomy". *Am. J. Surg.* 106: 206.
- Schofield, P. F., Watson-Williams, E. J. and Sourell, V. F. (1967). "Vagotomy and Pyloric Drainage for Chronic Duodenal Ulcer". *Arch. Surg.* 95: 615.
- Schuberth/

- Schuberth, O. and Westerholm, P. (1965). "Vagotomy and Antral Resection in the Surgery of Duodenal Ulcer". *Acta Chir. Scand.* 129: 530.
- Sharick, P. R. and Campbell, D. A. (1951). "Gastric Secretory Response to Insulin Hypoglycaemia: Influence of Insulin Dosage and Blood Sugar Level". *Am. J. Med. Sci.* 221: 364.
- Silen, W., Peloso, O. and Jaffe, B. F. (1966). "Kinetics of Intestinal Epithelial Proliferation: Effect of Vagotomy". *Surgery*, 60: 127.
- Sircus, W. (1965). "Prolonged Augmentation of the Maximal Secretory Responses of Canine Gastric Pouches by Chronic Obstruction: A Preliminary Report and Hypotheses". *Amer. J. Dig. Dis.* 10: 499.
- Sircus, W., Huston, C. J. W., Preshaw, R. M., Bassae, H. and Harkness, R. A. (1963). "Studies in Dogs on the Biphasic Nature of the Gastric Secretory Response to Hypoglycaemia and Other Stimuli with Special Reference to the Role of the Adrenals". *Gut*, 4: 42.
- Small, W. P. (1964). Ch.M. Thesis, University of Edinburgh, Ch. 5, p. 81.
- Smith, A. N. and Ridgeway, M. (1962). "Motility in the Small Intestine, Studied by the Telemetering Capsule" - In - 'Surgical Physiology of the Gastrointestinal Tract' Ed. A. N. Smith, Roy. Coll. Surg. Edin. p. 125.
- Smith, G. P., Brooks, F. P., Davis, R. A. and Rothman, S. S. (1960). "Fasting Gastric Contents in the Spider Monkey". *Am. J. Physiol.* 199: 889.
- Smithwick, R. H., Farmer, D. A. and Harrower, H. W. (1963). "Some Comments on Recurrent Ulceration after various Operations for Duodenal Ulcer based upon the Acidity and Peptic Activity of the Gastric Contents". *Am. J. Surg.* 105: 375.
- Snyder, M. A., Mahoney, E. B. and Robb, C. G. (1967). "Symptomatic Coeliac Artery Stenosis due to Constriction by the Neurofibrous Tissue of the Coeliac Ganglion". *Surgery*, 61: 372.

Soergel/

- Soergel, K. H. (1967). "Inert Markers". *Gastroenterology*, 54: 449.
- Stempien, S. J., French, J. D., Dagradi, A. E., Movius, H. J. and Porter, R. W. (1958). "The Early and Delayed Phases of Gastric Acid Secretion in Response to Insulin Hypoglycaemia". *Gastroenterology*, 34: 111.
- Stempien, S. J., Lee, E. R. and Dagradi, A. E. (1968). "Clinical Appraisal of Insulin Gastric Analysis". *Am. J. Dig. Dis. N.S.* 13: 21.
- Sun, D. C. H. and Shay, H. (1960). "Mechanism of Action of Insulin Hypoglycaemia on Gastric Secretion in Man". *J. Appl. Physiol.* 15: 697.
- Swann, J. (1834). "A Demonstration of the Nerves of the Human Body". Longman, Rees. London.
- Tanner, N. C. (1966). "A Technique of Selective Vagotomy". *Brit. J. Surg.* 53: 185.
- Thein, M. P. and Schofield, B. (1959). "Release of Gastrin from the Pyloric Antrum Following Vagal Stimulation by Sham Feeding in Dogs". *J. Physiol.* 148: 291.
- Thomas, D. G. and Duthie, H. L. (1966). "Use of 2-deoxy-D-glucose to test for the Completeness of Surgical Vagotomy". *Gut*, 9: 125.
- Uvnas, B. (1942). "The Part Played by the Pyloric Region in the Cephalic Phase of Gastric Secretion". *Acta Physiol. Scand.* 4: Suppl. XIII, 1942.
- Uvnas, B., Emas, S., Fyro, B. and Sjodin, L. (1966). "The Interaction between Vagal Impulses and Gastrin in the Control of Gastric Acid Secretion". *Am. J. Dig. Dis.* 11: 103.
- Visick, A. H. (1948). "The Study of Failures After Gastrectomy". *Ann. R. Coll. Surg.* 3: 266.
- Waddell, W. R. (1956). "Effect of Antrum Exclusion on Gastric Secretion". *J. Appl. Physiol.* 9: 22.

Waddell/

- Waddell, W. R. (1957). "The Acid Secretory Response to Histamine and Insulin Hypoglycaemia after Various Operations on the Stomach". *Surgery*, 42: 652.
- Waddell, W. R. and Wang, C. C. (1952). "Effect of Vagotomy on Gastric Evacuation of High Fat Meals". *J. Appl. Physiol.* 5: 705.
- Walters, W. and Mobley J. E. (1957). "Five to Ten Year Follow-up of 162 Cases of Duodenal Ulcer treated by Vagotomy with and without Associated Gastric Operations". *Ann. Surg.* 145: 753.
- Wastell, C. and Ellis, H. (1966). "Faecal Fat Excretion and Stool Colour after Vagotomy and Pyloroplasty". *Brit. Med. J.* 1: 1194.
- Weinstein, V. A., Hollander, F., Lauber, F. U. and Colp, R. (1950). "Correlation of Insulin Test Studies and Clinical Results in a Series of Peptic Ulcer Cases Treated by Vagotomy". *Gastroenterology*, 14: 214.
- Wheeler, H. B., Hoar, C. S. Jr., and Curtis, L. E. (1966). "Measured Subtotal Gastrectomy for Duodenal Ulcer: Size of Resection Versus Ulcer Control and Patient's Rehabilitation". *Arch. Surg.* 92: 52.
- White, T. T., McAlexander, R. A. and Magee, D. F. (1962). "Gastro-pancreatic Reflex After Various Gastric Operations". *Surg. Forum.* 13: 286.
- White, T. T., Lundh, G. and Magee, D. F. (1960). "Evidence for the Existence of a Gastro-pancreatic Reflex". *Amer. J. Physiol.* 198: 725.
- White, T. T., Lenninger, S. G., Elmslie, R. G. and Magee, D. F. (1966). "Effect of Truncal and Selective Vagotomy on Duodenal Aspirates in Man: Amylase, Protease and Lipase Response to Secretin and Pancreozymin Stimulation". *Ann. Surg.* 164: 257.
- Whittaker, L. D., Judd, E. S. and Stauffer, M. H. (1967). "Analysis of Use of Vagotomy with Drainage Procedure in Surgical Management of Duodenal Ulcer". *Surg. Gynae. Obst.* 125: 1019.

Whittle/

- Whittle, M. W. (1968). "The Effect of Bile Salts on Polyethylene Glycol Assay". Communication to Surgical Research Society, London.
- Williams, E. J. and Irvine, W. T. (1966). "Functional and Metabolic Effects of Total and Selective Vagotomy". *Lancet*, 1: 1053.
- Williams, J. A. and Cox, A. G. (1969). "After Vagotomy". Butterworths, London.
- Worning, H. and Amdrup, E. (1965). "Experimental Studies on the Value of the Reference Substances Polyethylene Glycol, Bromsulphthalein, and 51-Cr as Indicators of the Fluid Content of the Intestinal Lumen". *Gut*, 6: 487.
- Zierler, K. L. (1959). "Possible Mechanisms of Insulin Action on Membrane Potential and Ion Fluxes". *Am. J. Med.* 40: 735.

APPENDIX I

DOCUMENTATION OF ANATOMICAL STUDIES

AT OPERATION

APPENDIX IDocumentation of Anatomical Studies at Operation

A photocopy of the proforma used to compile anatomical information is shown on the following page. Surgeons, or their first assistants, were asked to complete the proforma as soon as possible after operation. The proforma shows a typical record. This patient, Mr. R.M., underwent selective vagotomy and gastro-enterostomy by Mr. C.W.A. Falconer on 12.6.68.

Patient's name *Muller* Ward *D7*Operation *SV & GE* Date *12/6/68*Surgeon CWAF = 1 CVR * 4
WPS = 2 Other (specify)
ANS = 3 = 5

Patient's habitus

lean = 1, average = 2, obese = 3

SURGICAL ANATOMY AS SEEN AT OPERATION.ANTERIOR VAGUS.

Anatomy not clear

Main trunk. single = 1

multiple and separate = 2

multiple but joining at or above

cardia = 3

Hepatic division

single bundle = 1

slightly separated strands = 2

widely separated strands = 3

POSTERIOR VAGUS.

Anatomy not clear.....

Main trunk Single = 1

double = 2

Coeliac Division.

clearly seen = 1

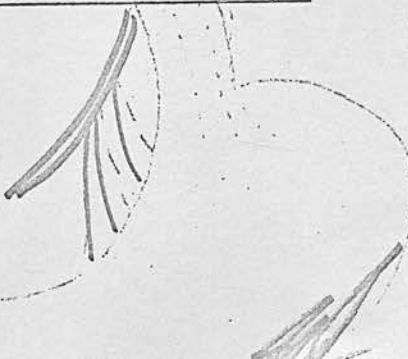
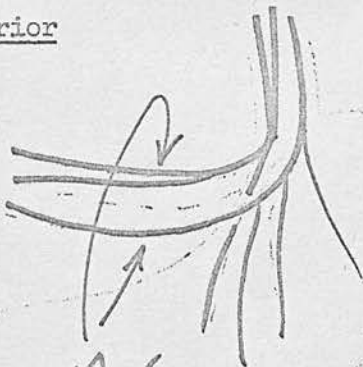
palpated but not seen = 2

Any other anatomical feature .. specify *large hepatic*
*artery from Q gastric artery*Exploration of the lower oesophagus Not done = 0

Done but no extra fibres found = 1; done and extra fibres

found = 2. *Sent for histology.*

Was the lower oesophagus thoroughly explored? Yes = 1, no = 0

Was the lower oesophagus and lesser curvature entirely cleared
of nerve and vessel connections? yes = 1, no = 0.AnteriorPosterior and lower oesophagus

APPENDIX II

THE TECHNIQUE OF CERVICAL OESOPHAGOSTOMY

APPENDIX IIThe Technique of Cervical Oesophagostomy

The type of cervical oesophagostomy employed in the animal experiments (Chapters 8, 10 and 11, and Appendix III) was a modification of that described by Komorov and Marks (1958). It is illustrated in Figures A, 1-4.

Under nembutal anaesthesia the dog's neck was shaved and cleaned with Cetavlon. A $1\frac{1}{2}$ " longitudinal incision was made, centred on a point 1 - $1\frac{1}{2}$ " to the left of the mid-line and 2 - 4" above the supra-sternal notch, depending upon the size of the dog.

Skin, subcutaneous tissues and platysma were incised and the strap muscles and sternomastoid retracted to expose trachea and oesophagus. The latter which lies slightly to the left of the trachea posteriorly was gently mobilised and brought forward to skin level. Interrupted 000 chromic catgut sutures were used in two layers to approximate a lozenge-shaped area of serosa, 1" in length, to platysma and skin (Fig. A, 1).

One week later the exposed oesophagus was incised longitudinally and the mucous membrane sutured to skin with interrupted 000 silk (Fig. A, 2).

The size of the oesophagostomy opening was important since too large an opening meant excessive loss of food and fluid during the process of eating and drinking. All the dogs were able to maintain or increase their body weight during the year of study.

/To

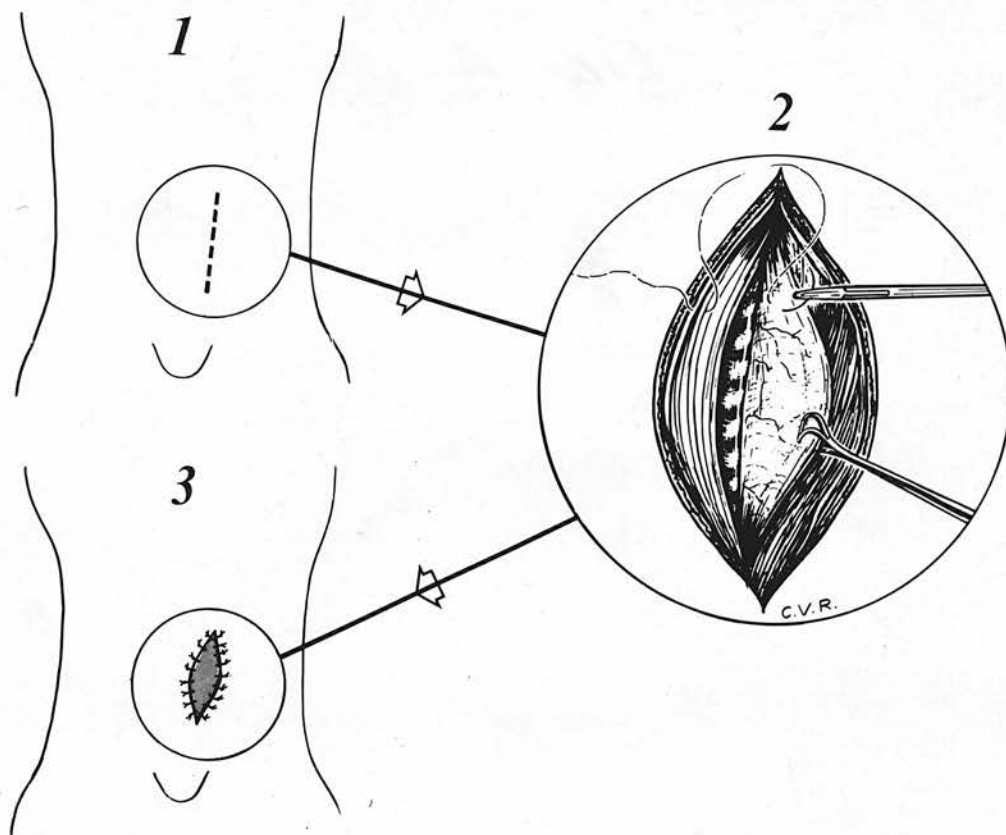


FIGURE A, 1. Steps in the construction of a cervical oesophagostomy in the dog. (1) The site of the skin incision. (2) Approximation of the oesophagus to the platysma and skin. (3) Completion of the first stage; the oesophagostomy is in place but not opened.

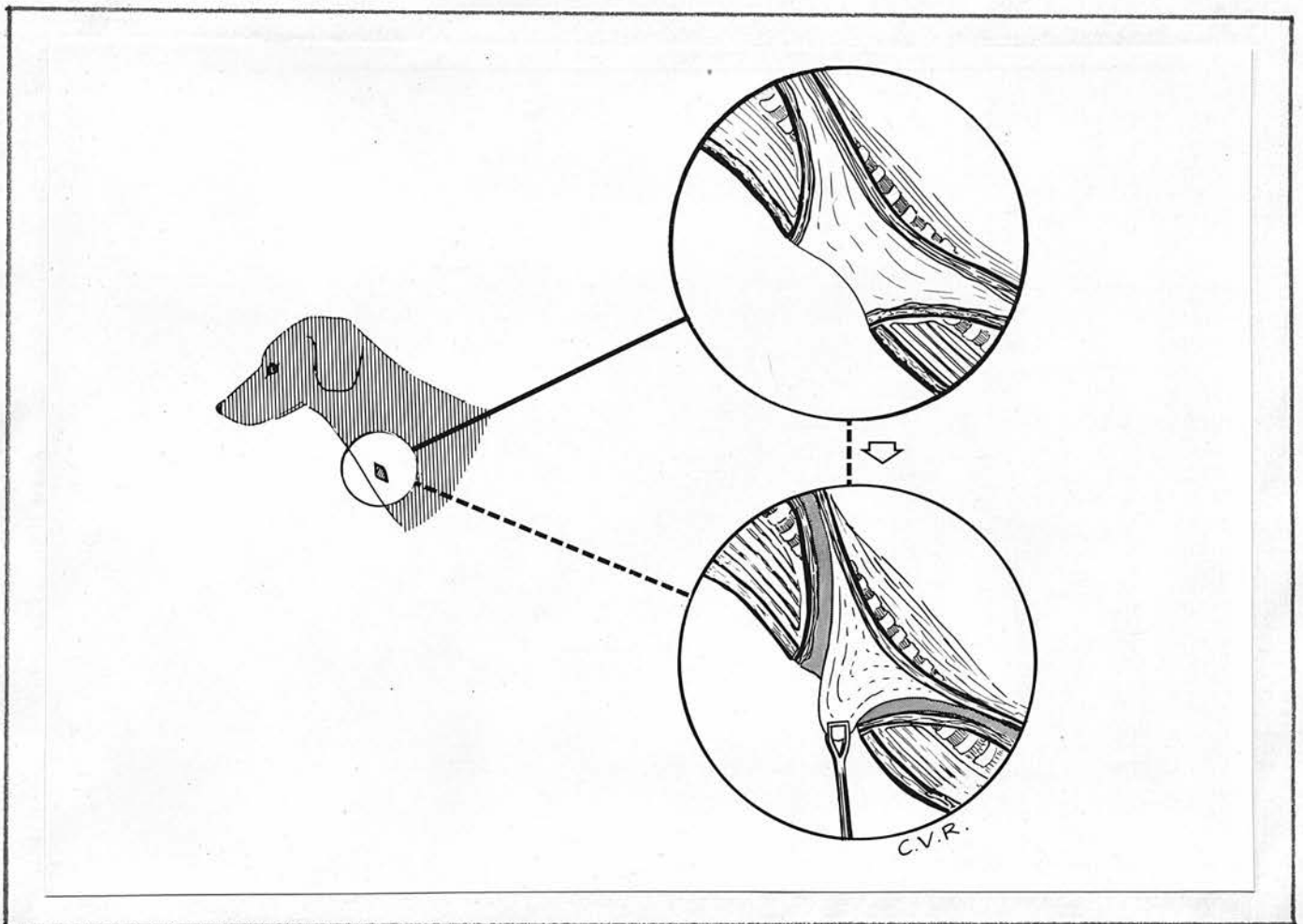


FIGURE A, 2. Cervical oesophagostomy in the dog. The lower inset shows the posterior mucous membrane being picked up with light tissue forceps in order to occlude the lumen during a gastric secretion test.

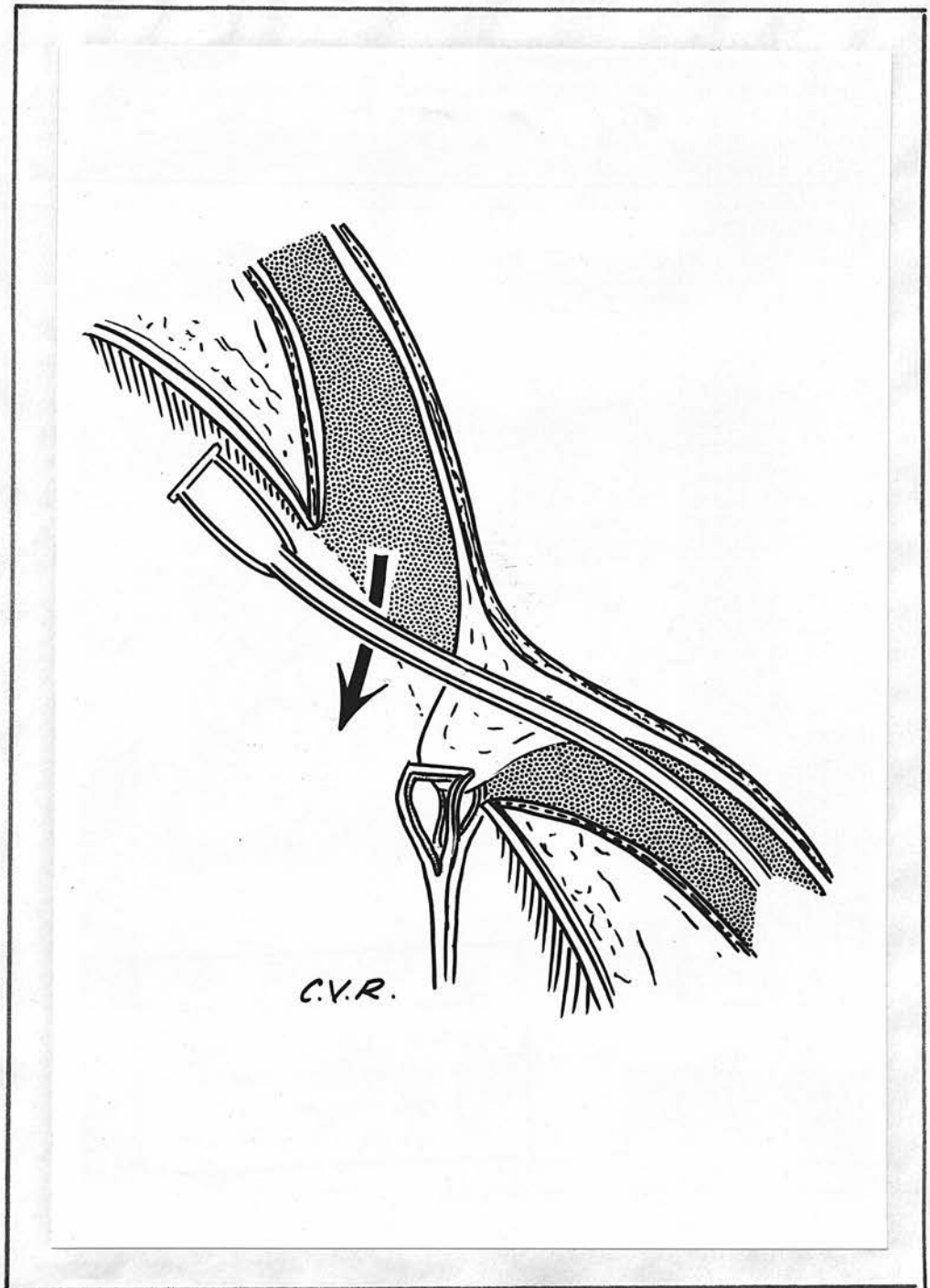


FIGURE A, 3. Diagram of the arrangement of the oesophagostomy during a gastric secretion test. The arrow shows the course taken by the saliva. A polyethylene cannula is in place for instillation of the recovery marker.



FIGURE A, 4. Photograph of the cervical oesophagostomy during an actual test. The tissue forceps hangs under its own weight and the effective deviation of saliva can be seen. The polyethylene cannula, for instillation of the recovery marker, is attached by adhesive tape to the animal's collar.

To occlude the oesophagus during a secretion test, in order to avoid contamination of gastric juice by saliva, the posterior wall of the oesophagus was picked up with light tissue forceps which, hanging under their own weight, effectively occluded the lumen without apparent discomfort to the animal (Figs. A, 2 and 3). The arrangement during a test and the deviation of the saliva is clearly shown in Figs. A, 3 and 4. This photograph also shows the polyethylene cannula (used for instilling polyethylene glycol) in place, held to the dog's collar with adhesive tape.

APPENDIX III

THE USE OF CARBON-14-LABELLED POLYETHYLENE

GLYCOL AS AN INDICATOR MARKER IN

POST-OPERATIVE SECRETION TESTS

APPENDIX IIIThe Use of Carbon-14-labelled Polyethylene Glycol as
an Indicator Marker in Post-Operative Secretion Tests.

The secretory studies described in Chapter 8 incorporated the use of a new method of measuring the recoveries of gastric juice. The experiment was unusual among studies of canine gastric secretion in that the use of a stomach-in-continuity preparation was preferred to a gastric pouch.

Difficulty in ensuring complete and uncontaminated collections has generally dictated the preference for pouch rather than whole-stomach preparations. The gastric pouch, however, carries disadvantages. Its construction and the maintenance of normal health over long periods may present difficulties. Fluid and electrolyte depletion may be a problem especially in the innervated pouch. The responses of pouch and of whole stomach to direct stimulants may not always be comparable. For example, it has been shown that while the maximal acid responses to histamine and gastrin in the canine vagally-denervated whole stomach are equal, histamine is the more potent stimulant of the Heidenhain pouch (Passaro and Grossman, 1964). Furthermore, atrophic changes may occur in the pouch mucosa so that true gastric function is not reflected in the data obtained and responses may deteriorate over a period of time (Ritchie and co-workers, 1966).

If continuity is preserved, recovery studies assume great importance in assessing the reliability of results. The clinical analogy is to the patient who has had gastric resection or drainage.

/Value

Value of secretory data is enhanced if loss through the pylorus or stoma can be measured.

Many substances have been used as markers in dilution and recovery studies of the gastro-intestinal tract (Heydn, 1956; Warning and Amdrup, 1965; Schedl, 1966). Polyethylene Glycol (PEG) has proved to be a highly satisfactory marker in terms of recovery (Maddrey and co-workers, 1967) but its chemical estimation (Malawer and Powell, 1967) may be time-consuming. The presence of bile in the gastric juice may interfere with the turbidimetric estimation of PEG (Whittle, 1968). This paper describes the use of carbon-14-labelled PEG as a marker for the assessment of gastric recoveries in the course of a study of vagally-stimulated secretion in dogs.

Materials and Methods

These data were obtained during the course of 131 insulin and 2-deoxy-D-glucose gastric secretion tests over a period of twelve months. Fifteen dogs were prepared with cervical oesophagostomies and gastric cannulae. The cannula was inserted through the gastric wall via a gastrostomy incision. In the case of the whole stomach, during the first phase of the experiment, the cannula was positioned 1 - 2" proximal to the Billroth I anastomosis. Cannulae were of two types. In five dogs a stainless steel cannula 6 cms. in length and 8 mm. internal diameter was used. In ten dogs a stainless steel and teflon cannula of adjustable length and 16 mm. internal diameter was inserted.

/The

The secretory study is described in Chapter 8. Suffice it to say that each test consisted of a one-hour basal and a two-hour post-insulin (or 2 deoxy-D-glucose) collection. The dogs were trained to stand quietly in frames with minimum restraint and the juice drained by gravity into clipped lengths of Penrose tubing, to be collected every seven-and-a-half minutes and pooled into fifteen-minute samples for purposes of titration.

Polyethylene-1, 2-¹⁴C-glycol was prepared by New England Nuclear Corporation with a specific activity of 0.115 mc/g and an approximate molecular weight of 4,600. The radioactivity of ¹⁴C-PEG was assayed by adding as much as 1 ml. of an aqueous solution (either standard solution or gastric content) to 10 - 15 ml. of Bray's solution and counting in a liquid scintillation spectrometer. For the assay of non-radioactive PEG the usual turbidometric procedure was employed.¹⁰

The relative molecular size of cold PEG-4000 (Union Carbide Company) was compared with that of ¹⁴C-PEG by gel filtration. The column (100 x 1.8 cm.) was packed with Sephadex G50 fine and the sample applied and eluted with phosphate buffer, pH 7, 0.05 M.

The PEG was instilled via a fine polythene cannula which was inserted through the oesophagostomy and secured by light adhesive to the dog's neck so that the tip of the cannula lay in the lower oesophagus (Fig.A3). Instillation was by slow intermittent

/injection

injection by hand syringe during the first one-and-a-half hours of the post-insulin period. Two millilitre aliquots were taken from each fifteen-minute sample and the radioactivity determined by counting in a Packard Tri-Carb scintillation counter. Recovery was calculated by totalling the counts obtained during each fifteen-minute sample and expressing the total as a percentage of the mean of two control samples taken from the PEG solution at the beginning of each test. During the series the volume of the infusate was randomly varied in order to determine whether this influenced the percentage recovered.

RESULTS*

Turbidometric Versus Radioactive Assay

The turbidometric assay of PEG in water, performed repeatedly by a careful, experienced technician varied considerably (Fig. A, 5). Repeated assays of radioactivity were reproducible with a much higher accuracy. The standard deviation of the mean was always less than 0.8% of the mean, when more than 500 counts per minute were used.

Gel Filtration

Radioactive PEG had a slightly larger molecular size than the cold PEG and was eluted from the column as a sharper peak suggesting a more uniform size (Fig.A, 6). To check stability this study was repeated six months later and the results were identical.

/Animal

*Information upon the turbidometric versus radioactive assay and the results of gel filtration was provided by Dr. F. Kern, Jr.

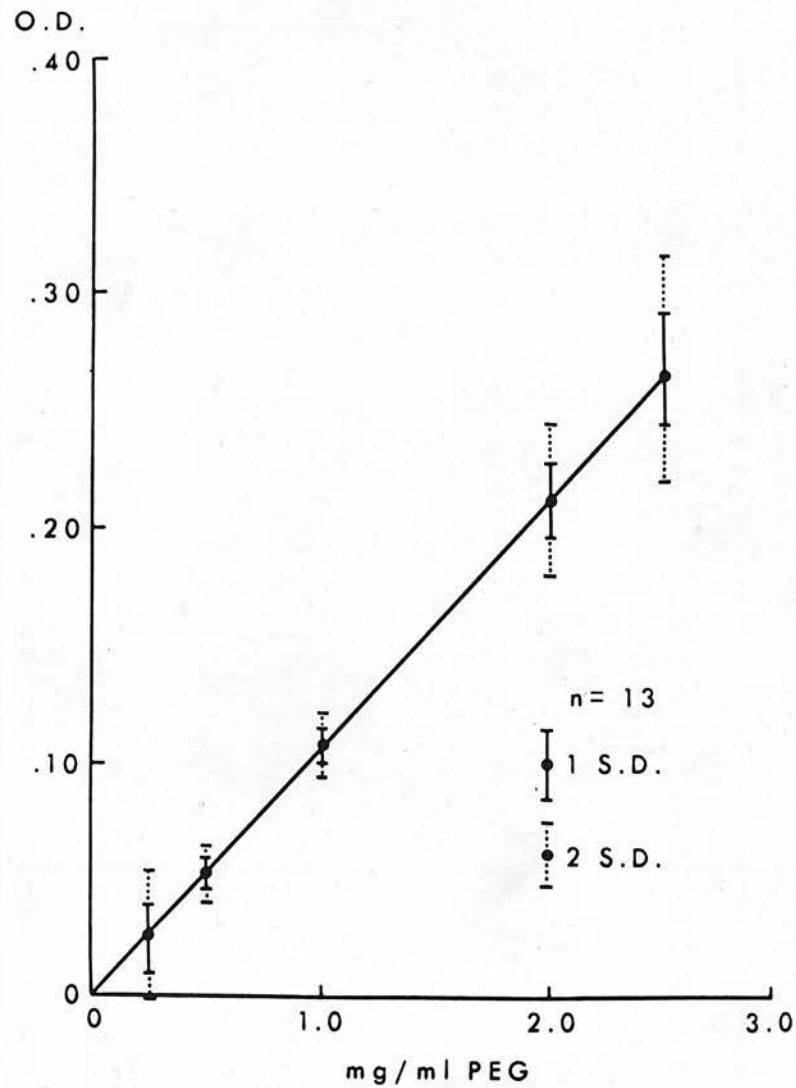


FIGURE A, 5. Multiple determinations of solutions of differing concentrations of polyethylene glycol as measured by the turbidimetric method.

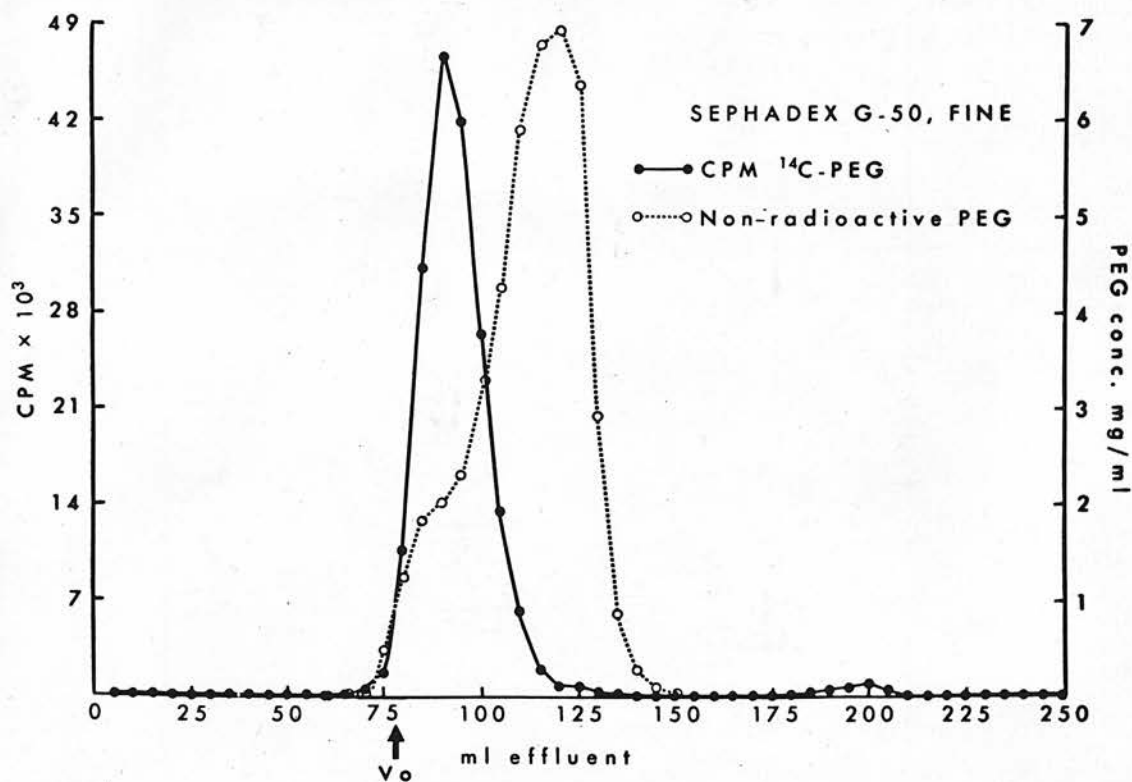


FIGURE A, 6. Gel-filtration of radioactive and non-radioactive polyethylene glycol (PEG) through a Sephadex column. The C-14 peak is shown on the left.

Animal Experiments

Fifty-two tests were carried out in 14 dogs with cannulated whole stomachs. Each dog underwent at least three tests. Twelve tests were carried out in two dogs which had pyloroplasty alone, eight in two with pyloroplasty and vagotomy, 56 tests in 10 dogs followed Billroth I partial gastrectomies and seven in four dogs followed partial gastrectomy combined with truncal vagotomy. The mean recoveries obtained for each of these categories are shown in Table 1. The highest mean recoveries were obtained from the group with whole stomachs ($86.2 \pm 1.8\%$). All groups except the partial gastrectomy plus vagotomy dogs showed mean recoveries in excess of 80%. Since this was a study of the effects of vagal stimulation it should be noted that the secretory output in the vagotomised animals was almost nil.

Table 2 shows the effects of varying the volume of the PEG solution. The best recoveries were obtained in the middle range of 10 - 15 mls. ($87.7 \pm \text{S.E. } 1.5\%$) significantly better recoveries were obtained in the latter group ($P = 0.02$). In practice the largest number of tests were performed using this intermediate range of volumes because larger amounts 20 - 25 mls. failed to provide any superior recovery ($85.9 \pm 3.6\%$).

In relating the gastric recoveries to the results of the secretion tests it was decided that tests showing an arbitrary recovery of less than 70% would be rejected and repeated. In terms

/of

TABLE A.1

CARBON - 14 LABELLED POLYETHYLENE GLYCOL RECOVERIES

Preparation	No. of Tests	Mean % Recovered	S. Error
Whole stomach	55	86.2%	$\pm 1.8\%$
Pyloroplasty	20	86.2%	$\pm 3.2\%$
Gastric resection	53	83.9%	$\pm 2.3\%$

TABLE A.2

THE EFFECT OF VARYING THE VOLUME OF INSTILLED C¹⁴ - PEG

Volume Infused	No. of Tests	Mean per cent recovery with standard error
1 - 5	29	80.0 \pm S.E. 3.3%
10 - 15	68	87.7 \pm S.E. 1.5%
20 - 25	13	85.9 \pm S.E. 3.6%

of the gastric preparation this resulted in the rejection of four out of 52 (7.8%) tests on dogs with whole stomachs, two out of 20 (10%) after pyloroplasty and 12 out of 62 (19.3%) after gastric resection. The effect of antrectomy in this study was to reduce by more than 50% the mean volume of juice produced in response to vagal stimulation. Recoveries appeared to be less satisfactory when secreted volumes were very low. When the secretory response was abolished by vagotomy and antrectomy the recoveries fell from a mean of $86.2 \pm \text{S.E. } 2.3\%$ in the control whole stomachs to a mean of $77.1 \pm \text{S.E. } 4.5\%$. This difference, however was not significant ($0.05 < P < 0.1$).

Discussion

The use of PEG as a marker has been discussed in a recent review by Søergel (1967). Well established as the substance most commonly cast in this role in gastro-intestinal studies, PEG has a low order of chemical reactivity, does not adhere to mucus, debris or food residues and is not absorbed from the stomach. Inferior recoveries in this study tended to be associated with small volumes of infusate (1 - 5 mls.) especially where there was little or no secretory response to a vagal stimulant after vagotomy and gastric resection. It is not known whether adhesion to tubing or mucosa, loculation among mucosal folds or loss via the anastomosis, or a combination of these factors, caused incomplete recovery. Despite these sources of loss, 60 tests (46.2%) provided recoveries of better than 90%, and only 18 (13.7%) were rejected because of recoveries falling below 70%.

/This

This study suggests that the use of a marker such as PEG is of value for the reliable interpretation of data derived from gastric preparations in which the secretions are being collected from a tract which remains in continuity; PEG labelled with carbon-14 combines the advantages of a well-tried marker substance with the ease and simplicity of radio-isotope technique. The satisfactory measurements obtained using 0.1 uc or less indicate that C-14-PEG is suitable for use in the human gastro-intestinal tract.

APPENDIX IV

GRAPHS OF SECRETORY DATA

OBTAINED FROM ANIMAL EXPERIMENTS

APPENDIX IV.GRAPHS OF SECRETORY DATA OBTAINED FROM ANIMAL EXPERIMENTS.

The following pages contain graphic representations of data provided in Part II, Chapter 8 and Part III, Chapter 10. The first thirteen graphs (pages 314 to 320) illustrate dose-response studies. They are not set out in strict numerical order because they were compiled during the experiment in the order in which the results became available.

The second section of this appendix presents graphs from Phases I and II of the study described in Chapter 8. Graphs are shown of data from control animals (4) with and without pyloroplasty and from the complete and incomplete antrectomy groups (5) at two different dose levels of insulin.

In every graph the means of at least three tests are shown with one standard deviation above and below the mean.

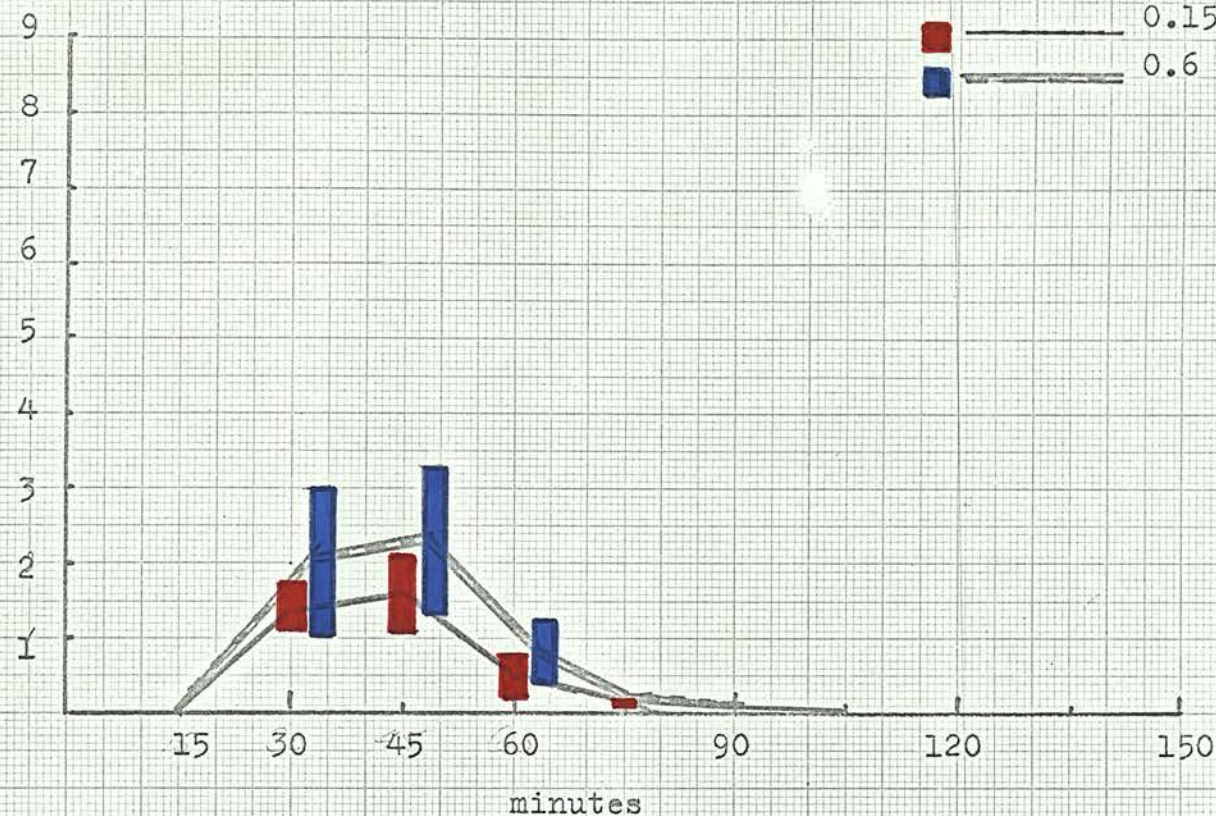
APPENDIX IV: SECTION I

The acid secretory response to insulin in doses of 0.15
and 0.6 u/kg body weight .

DOG # 20.

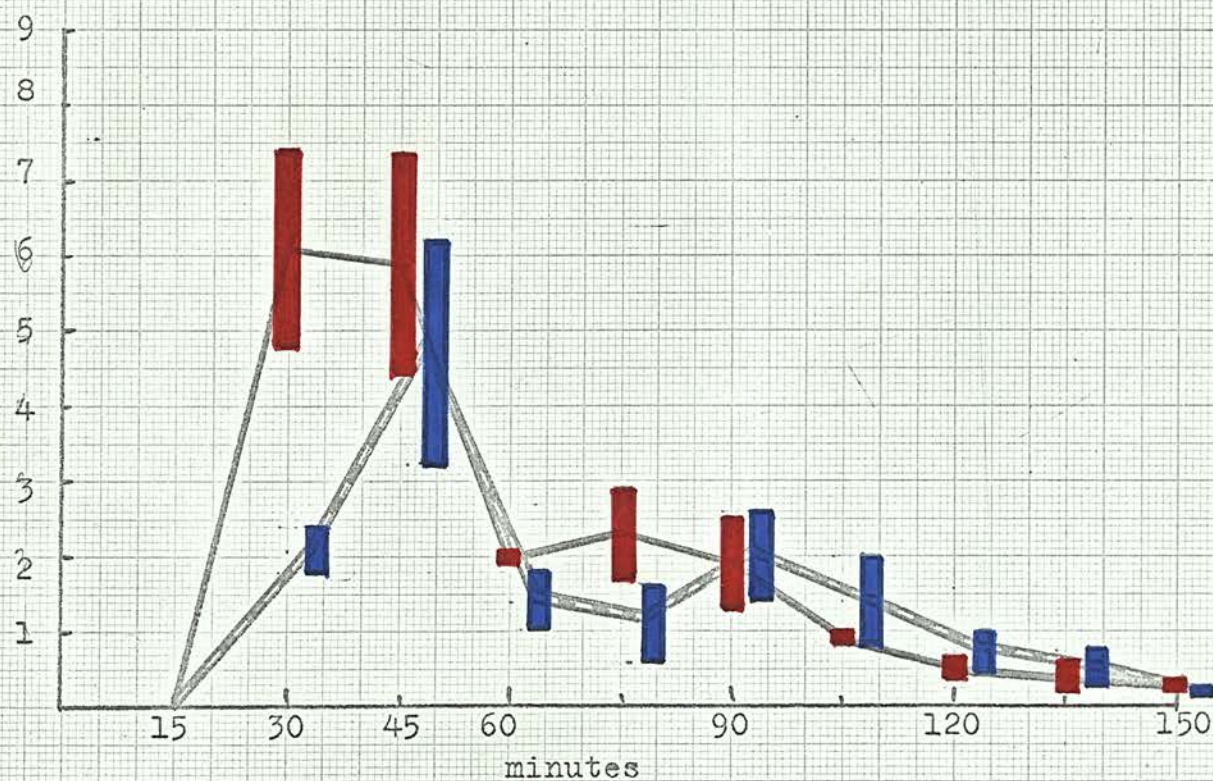
mEq

0.15u/Kg.
0.6 u/Kg.



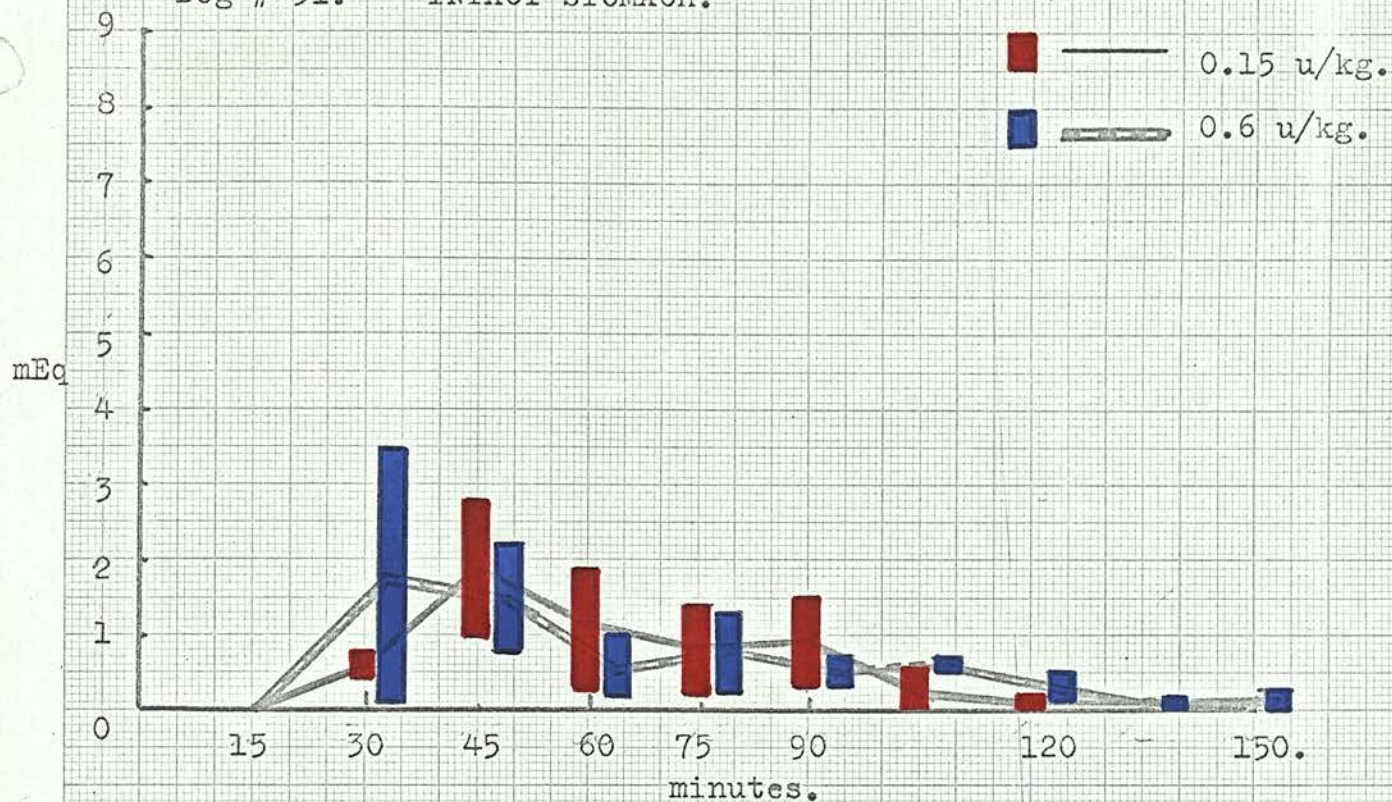
DOG # 116.

mEq

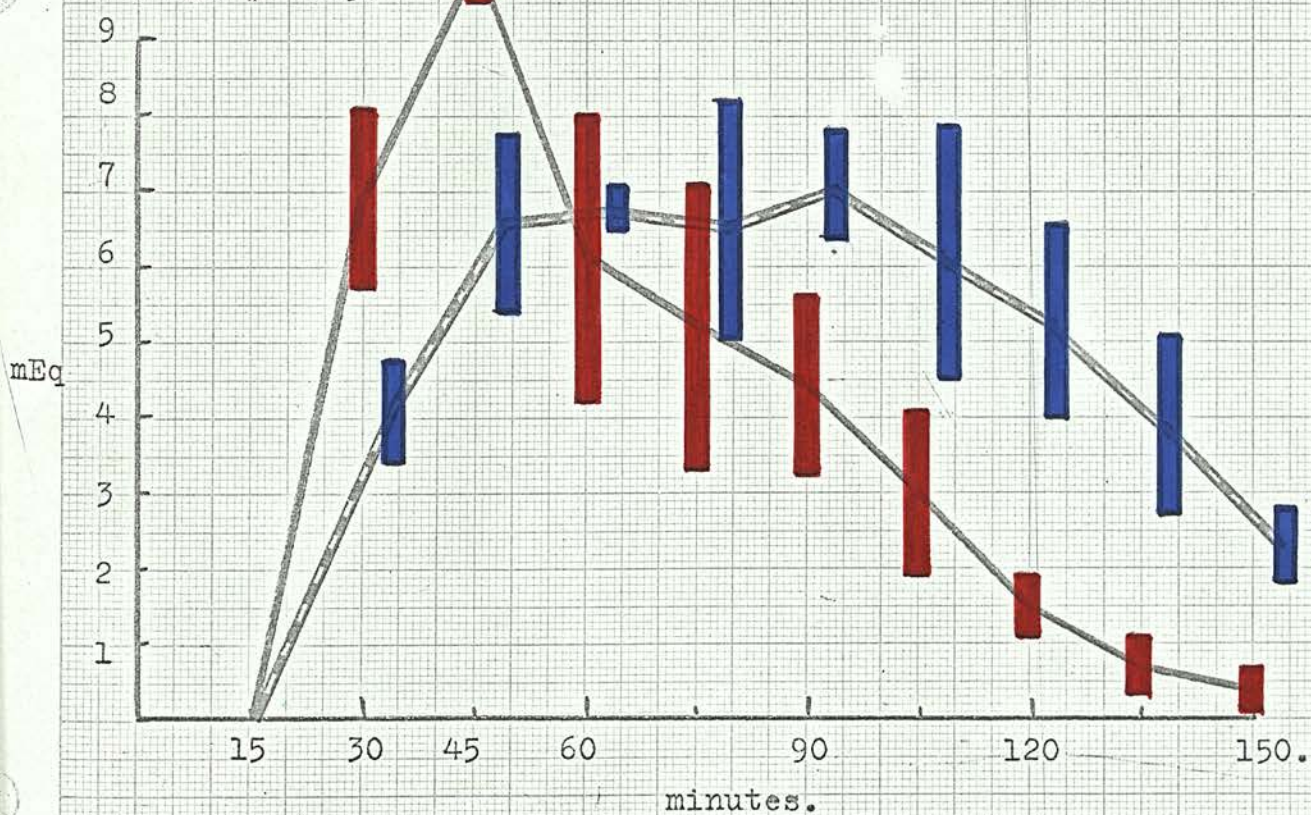


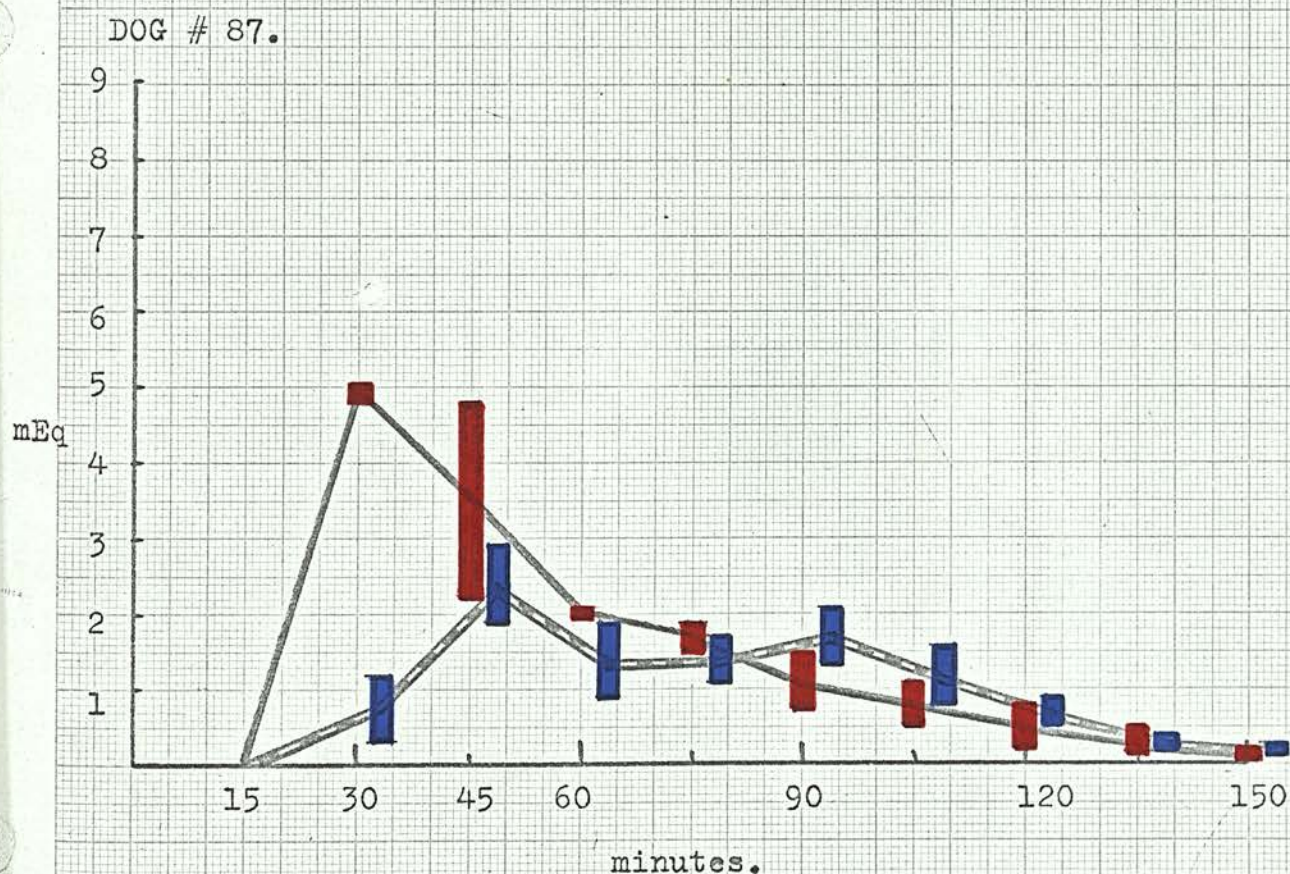
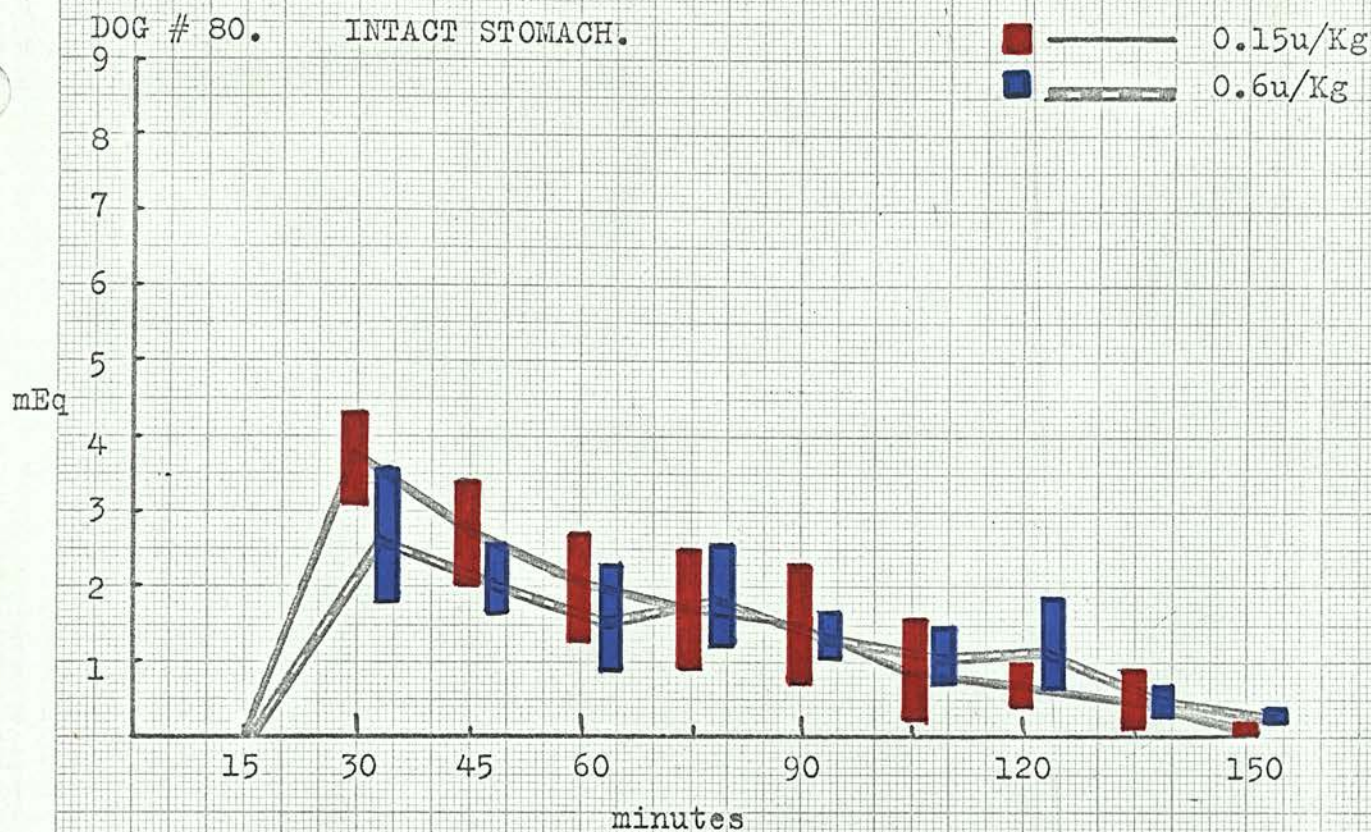
Dog # 31.

INTACT STOMACH.

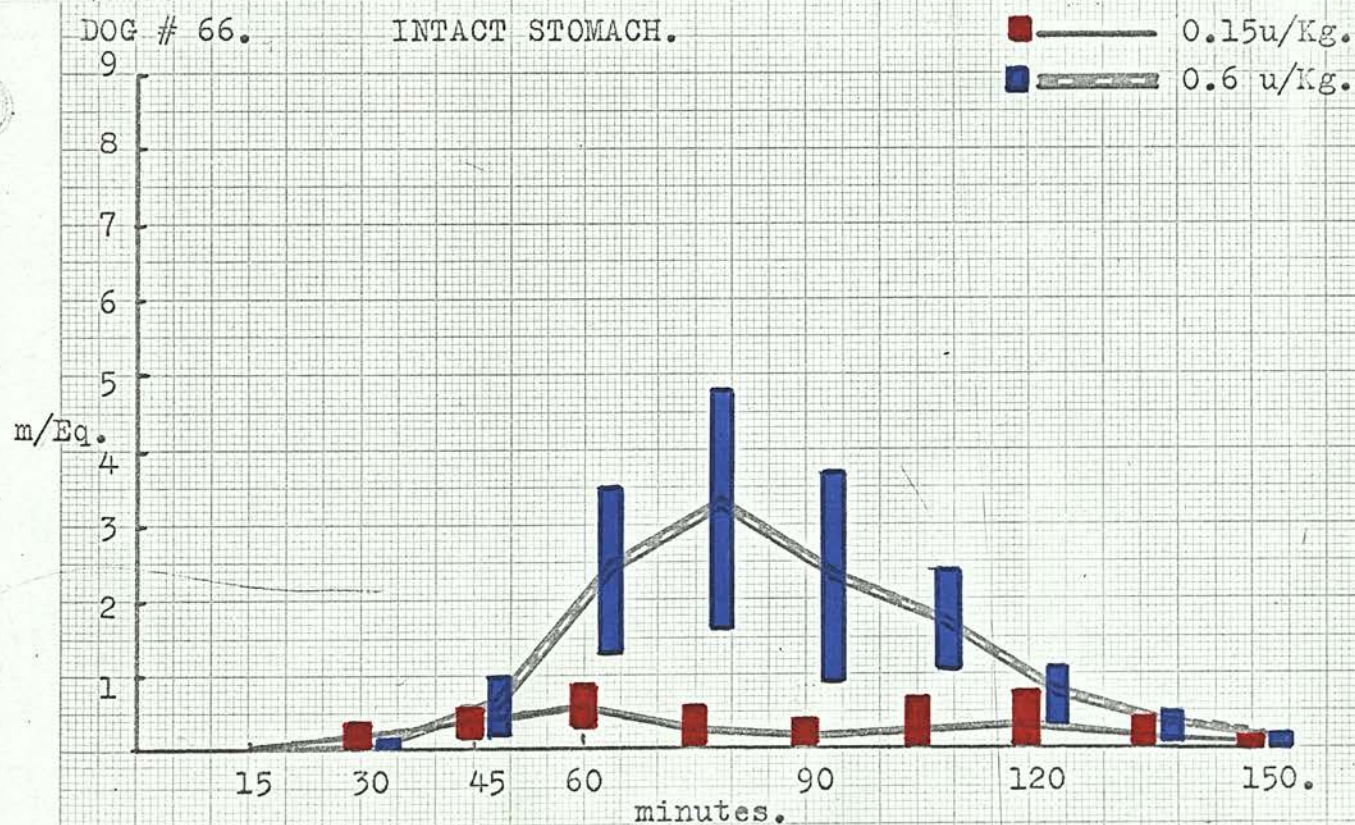
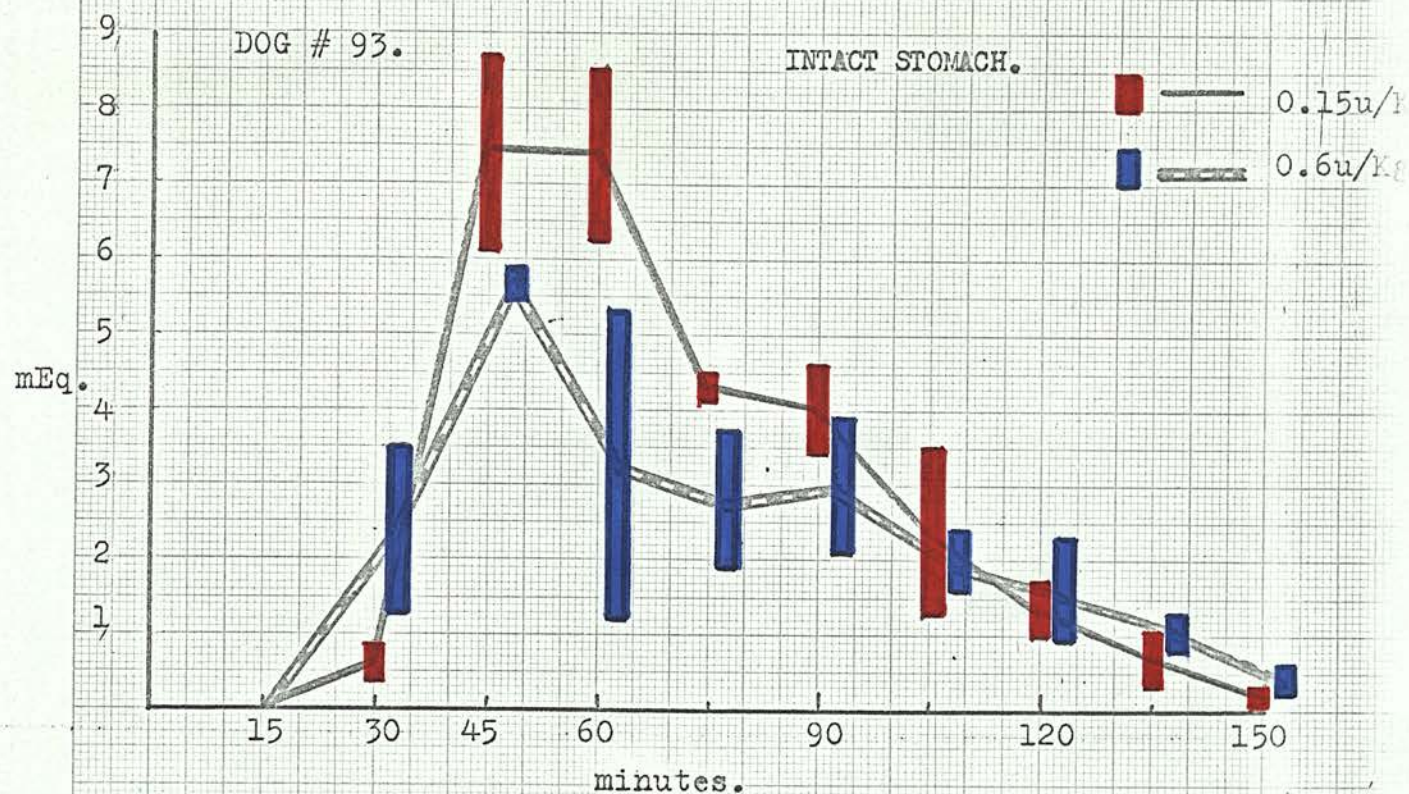


DOG # 149.





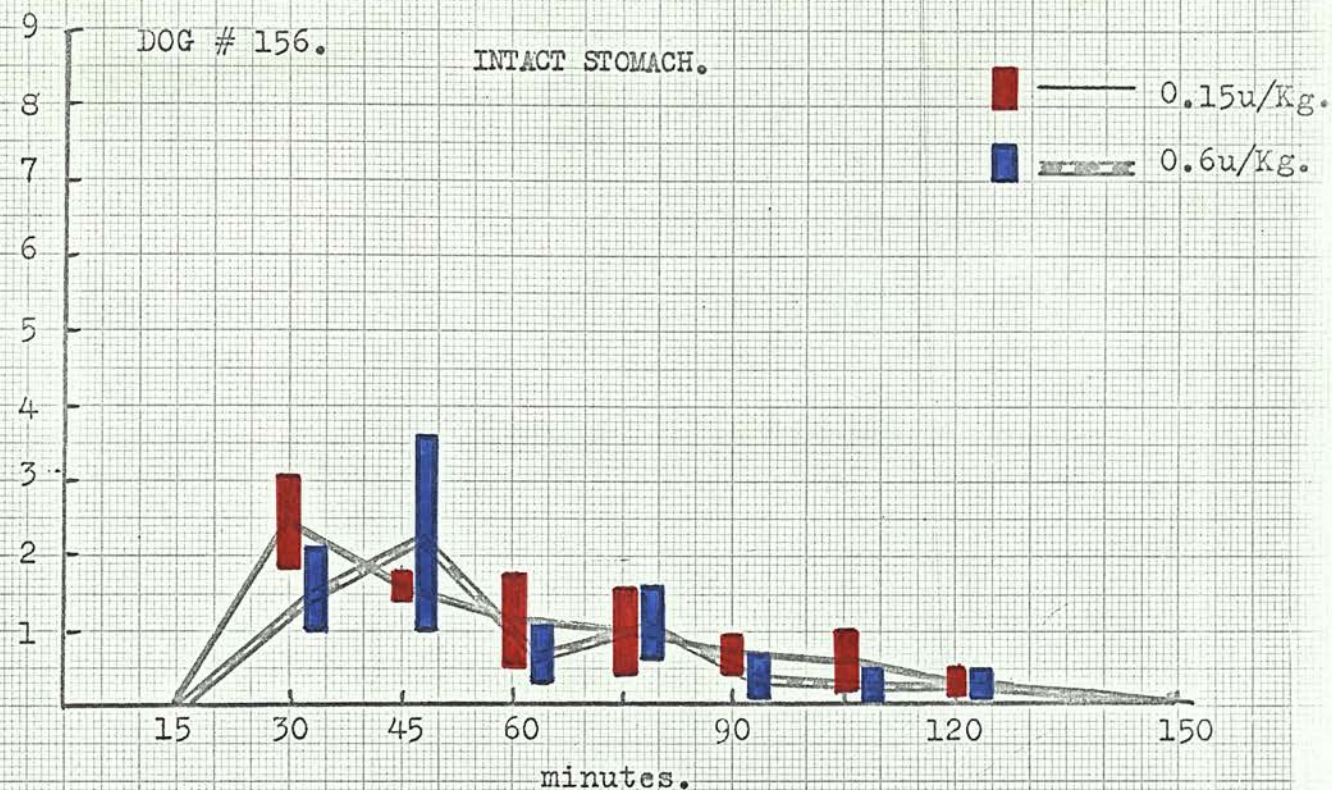
INSULIN STIMULATED SECRETION.



INSULIN STIMULATED SECRETION.

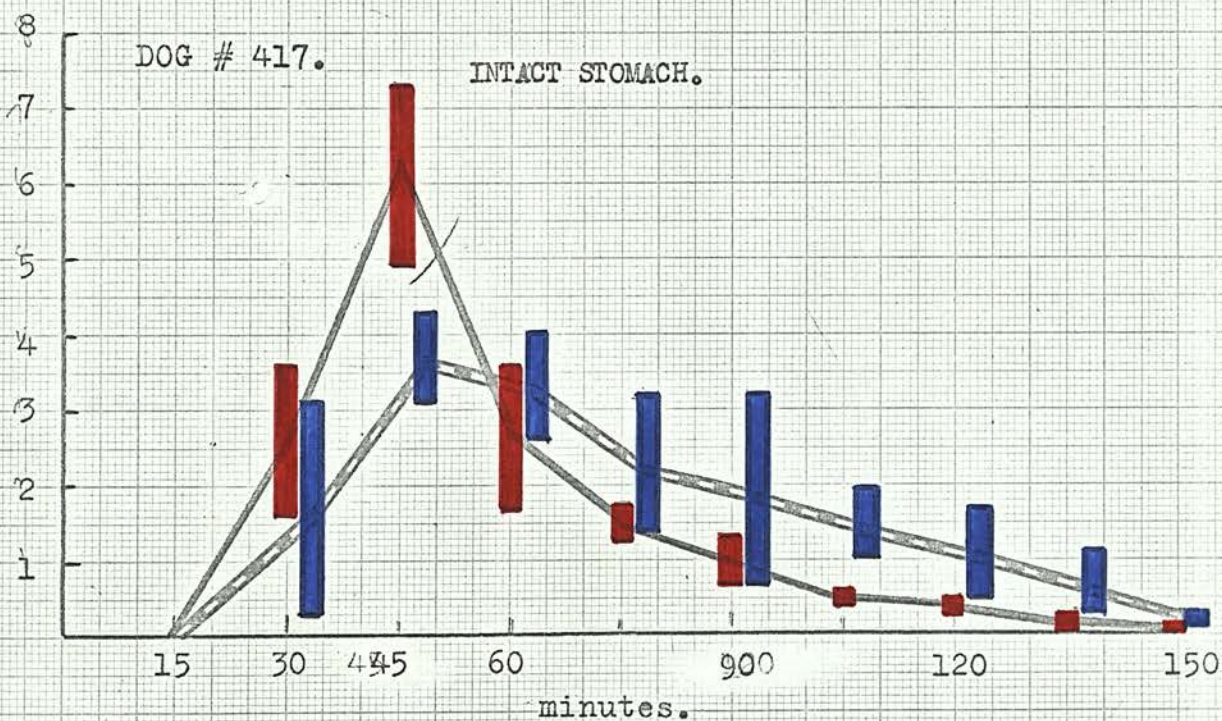
DOG # 156.

INTACT STOMACH.



DOG # 417.

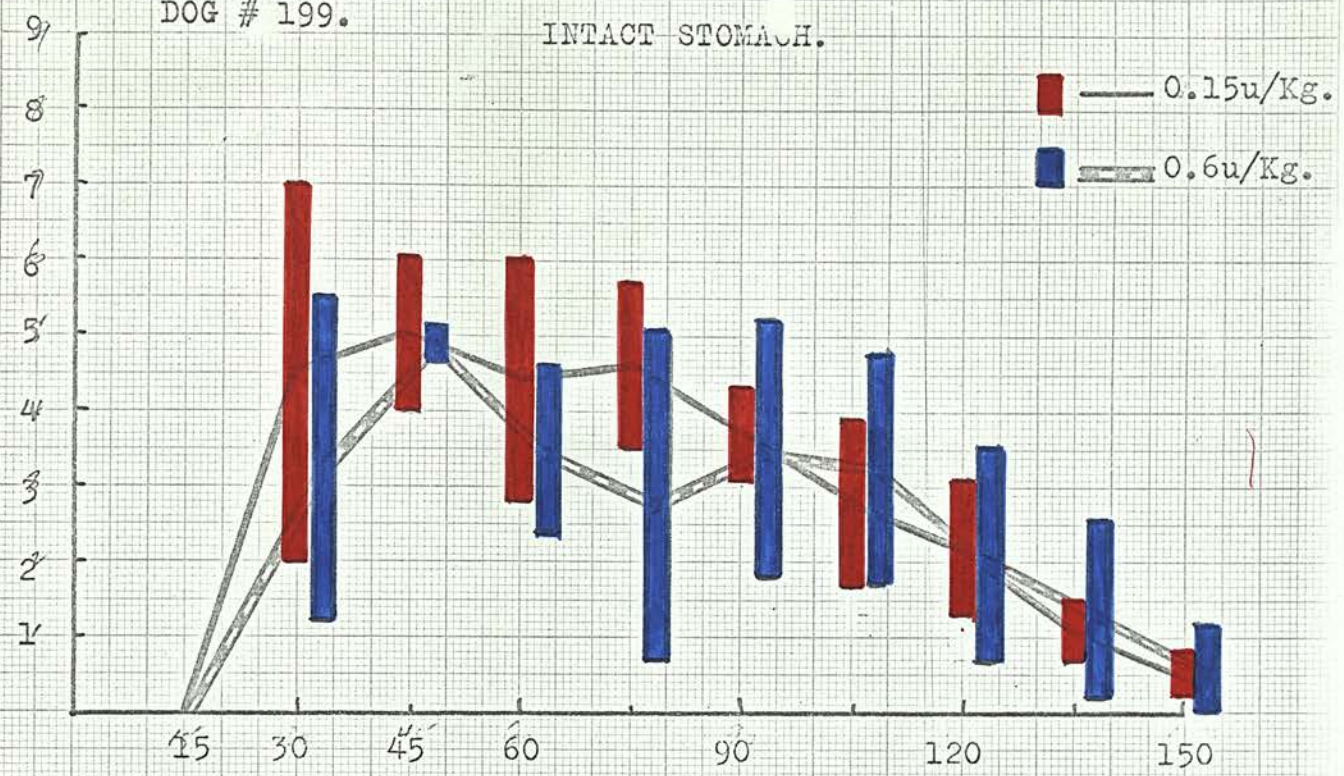
INTACT STOMACH.



INSULIN STIMULATED SECRETION.

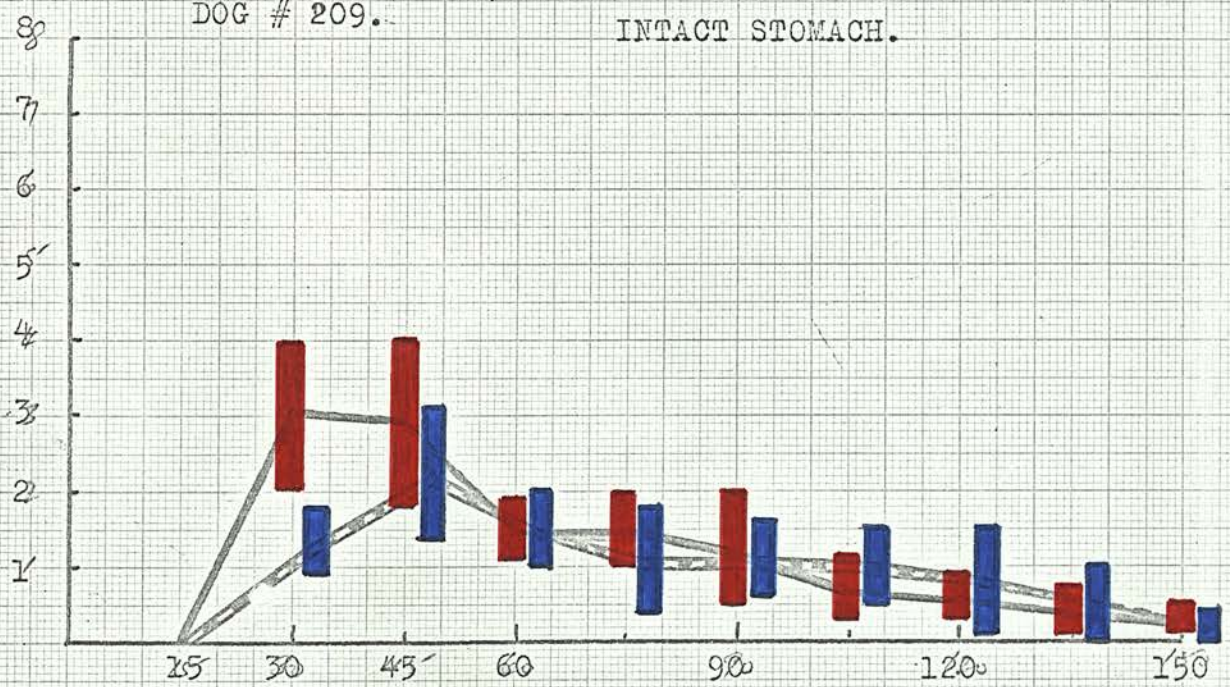
DOG # 199.

INTACT STOMACH.



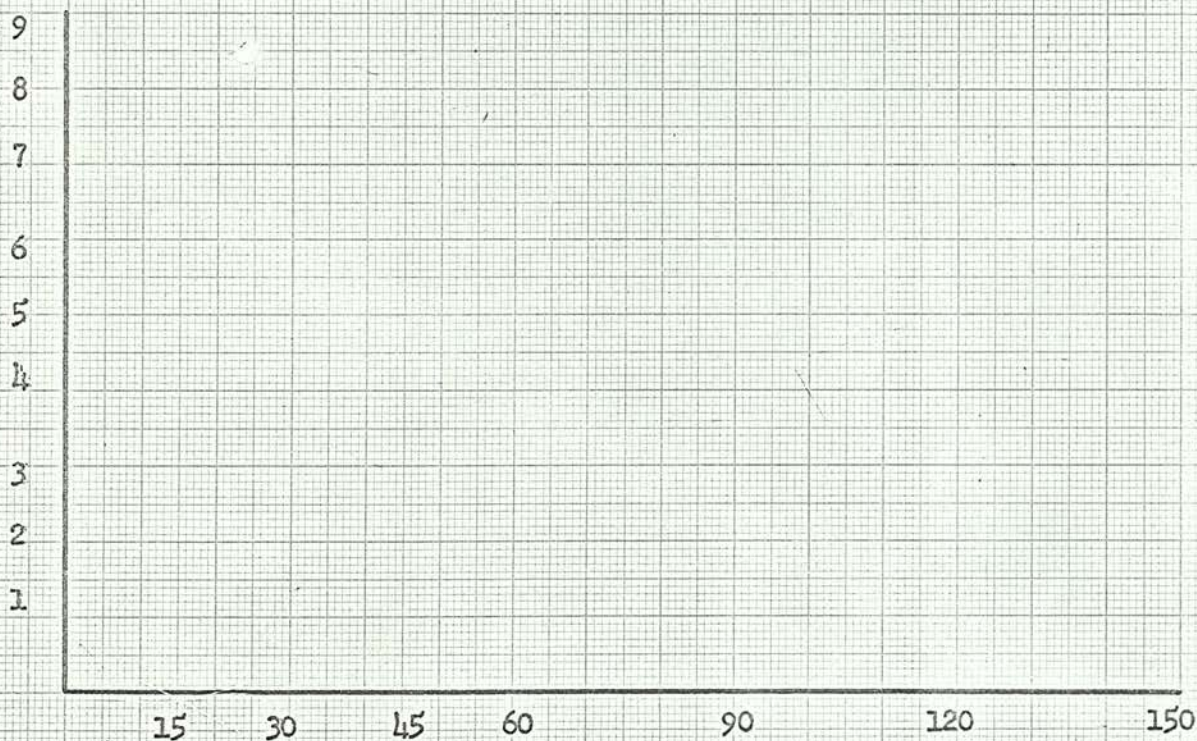
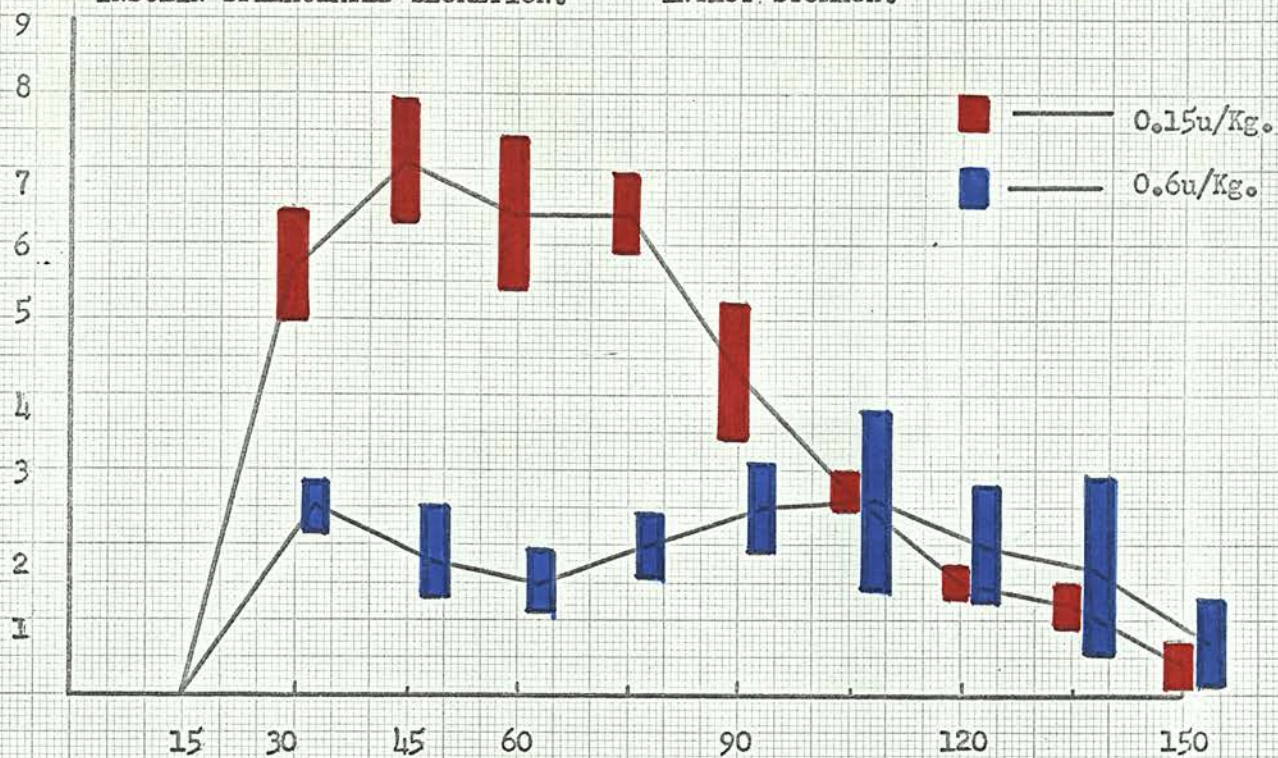
DOG # 209.

INTACT STOMACH.



INSULIN STIMULATED SECRETION.

INTACT. STOMACH.



APPENDIX IV: SECTION II

The acid secretory responses to two doses of insulin
before and after complete and incomplete antrectomy
and in control animals with and without pyloroplasty.

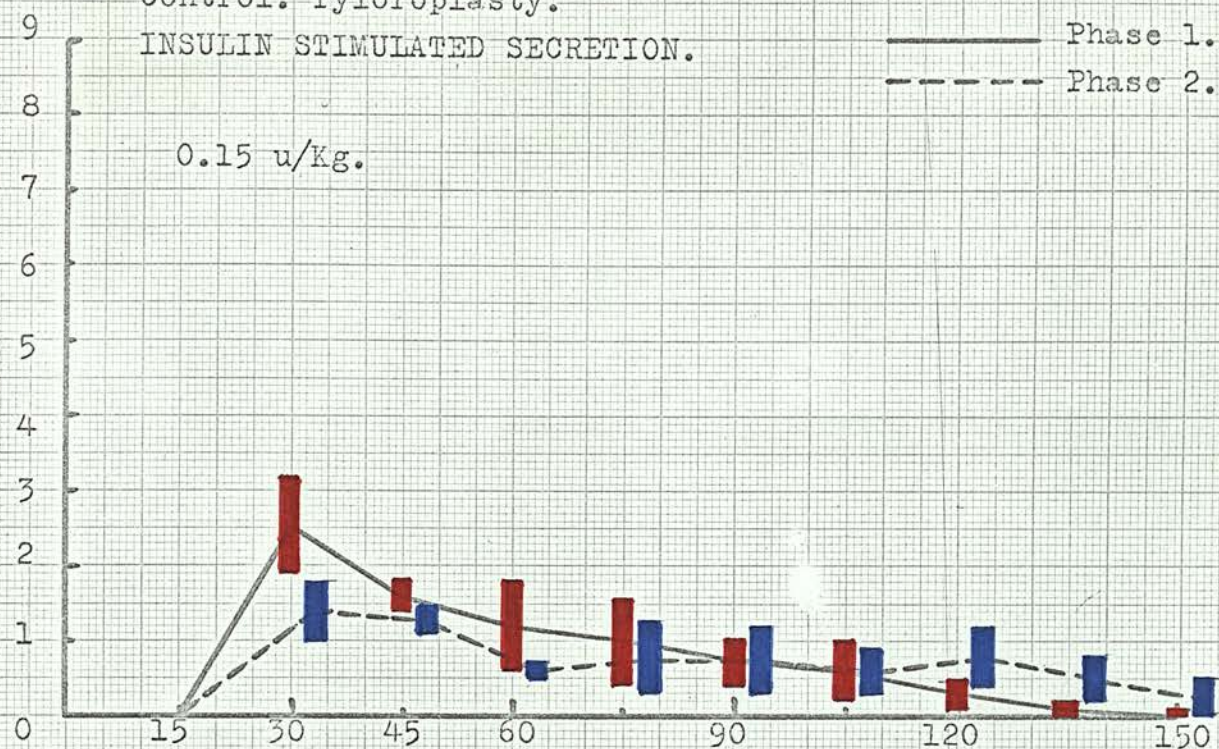
Control. Pyloroplasty.

INSULIN STIMULATED SECRETION.

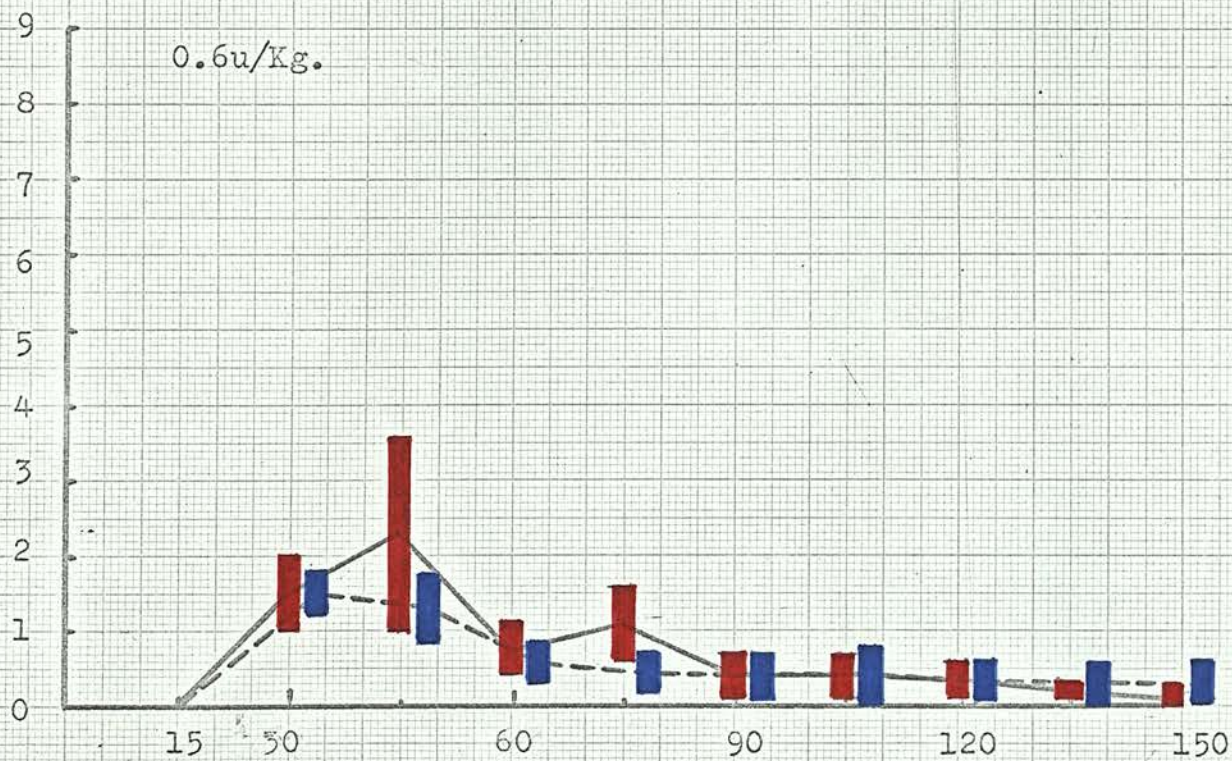
0.15 u/kg.

Phase 1.

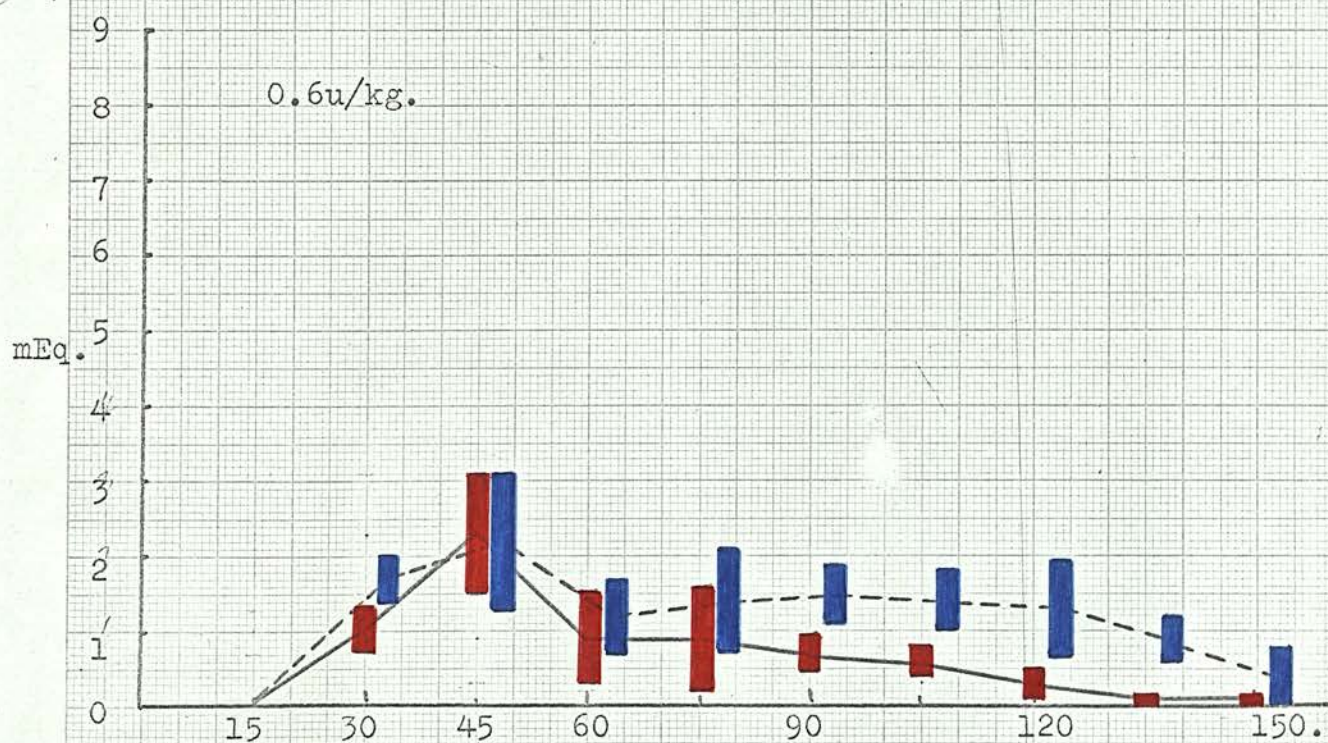
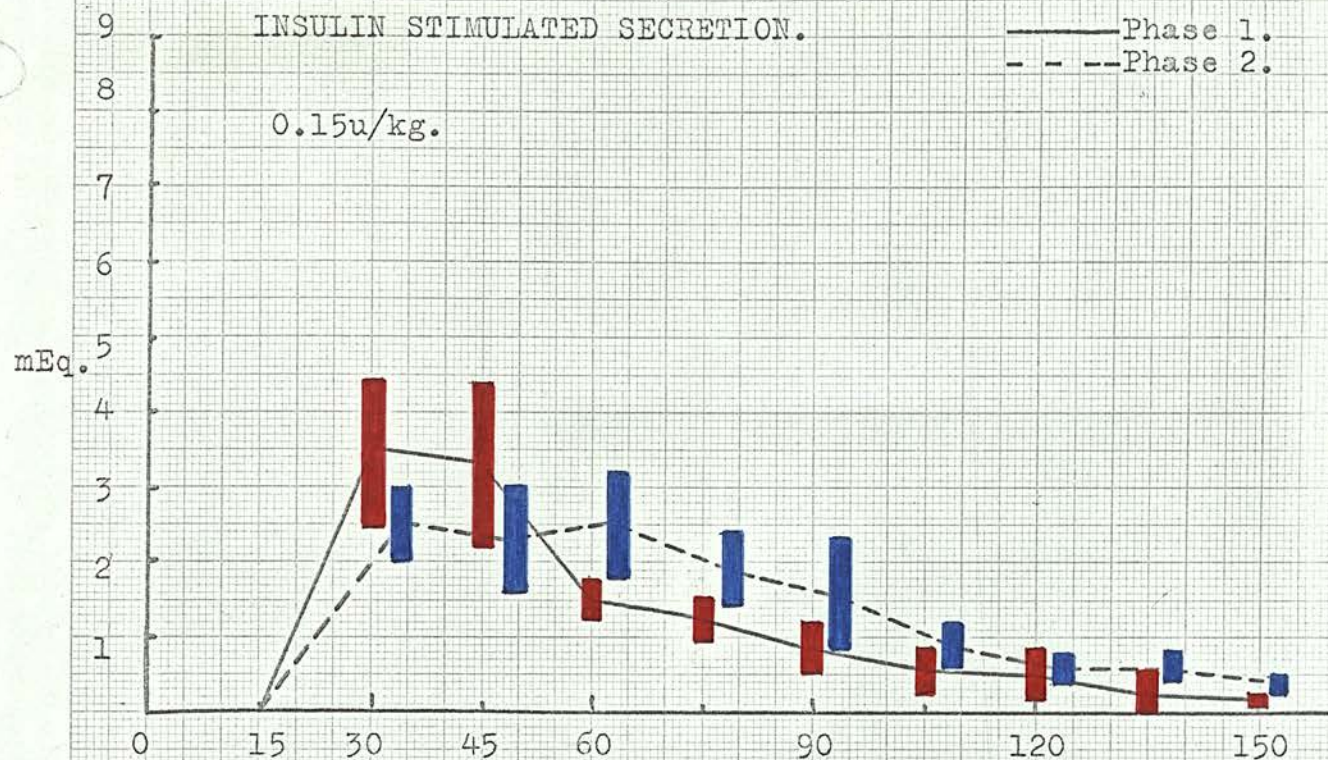
Phase 2.



0.6u/Kg.



Dog # 209. Control. Pyloroplasty.
INSULIN STIMULATED SECRETION.



DOG # 199. Control. No pyloroplasty.

C

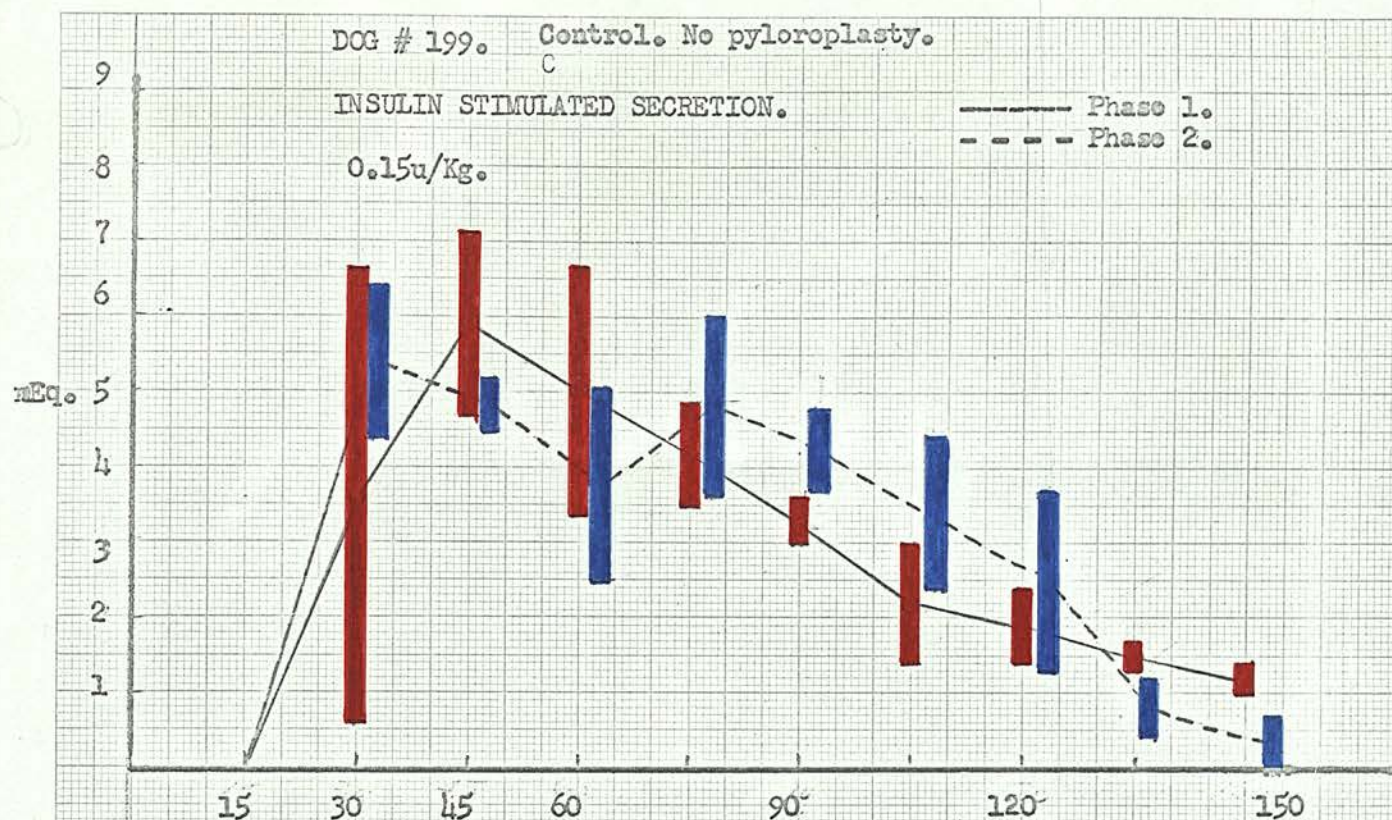
INSULIN STIMULATED SECRETION.

0.15u/Kg.

Phase 1.

Phase 2.

mEq.



0.6u/Kg.

9

8

7

6

5

4

3

2

1

15

30

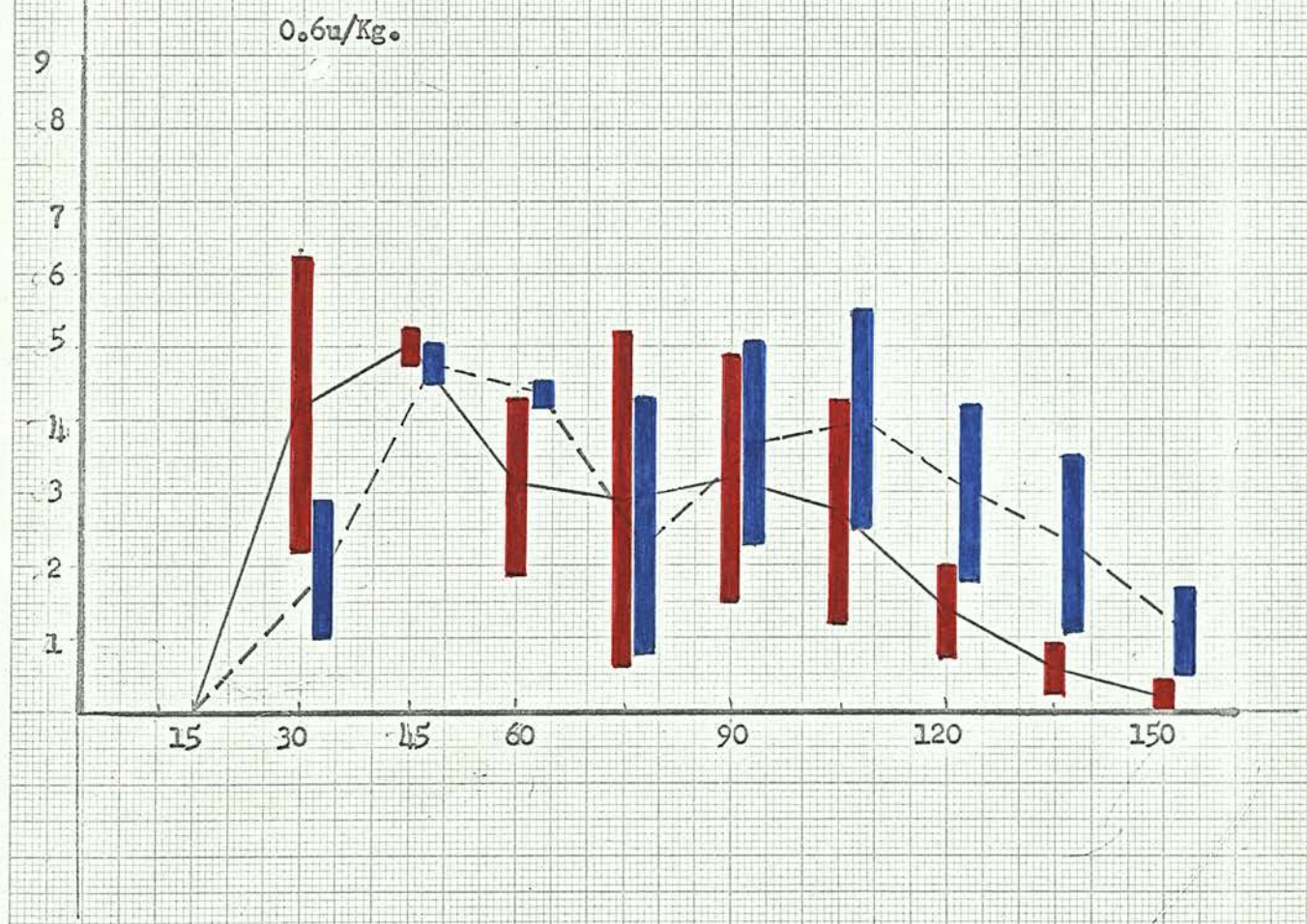
45

60

90

120

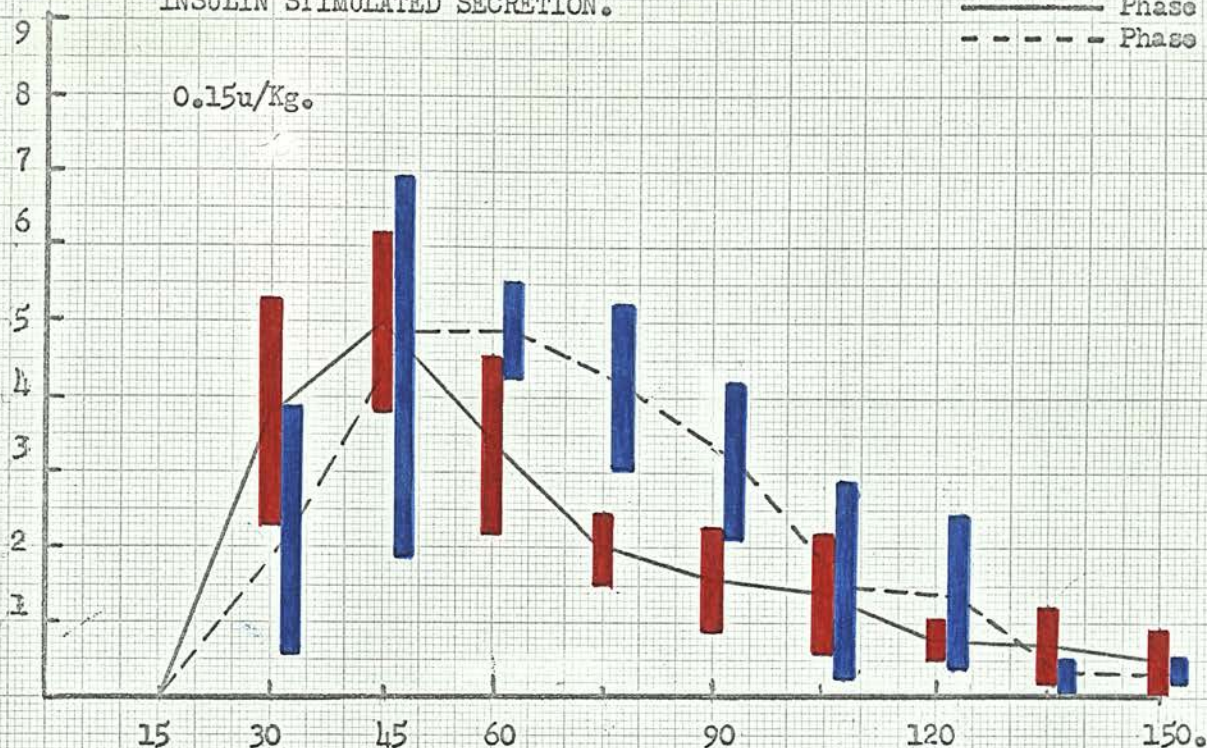
150



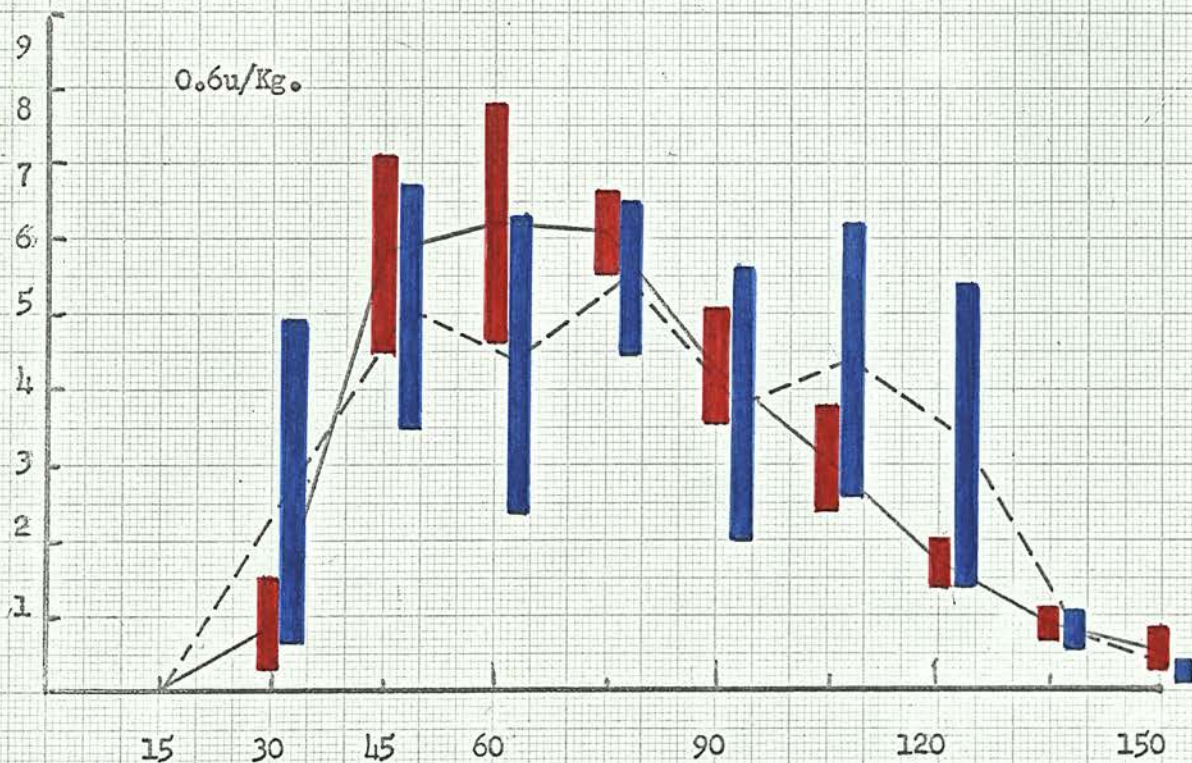
DOG # 375

CONTROL. NO PYLOROPLASTY.
INSULIN STIMULATED SECRETION.— Phase 1.
- - - Phase 2.

0.15u/Kg.

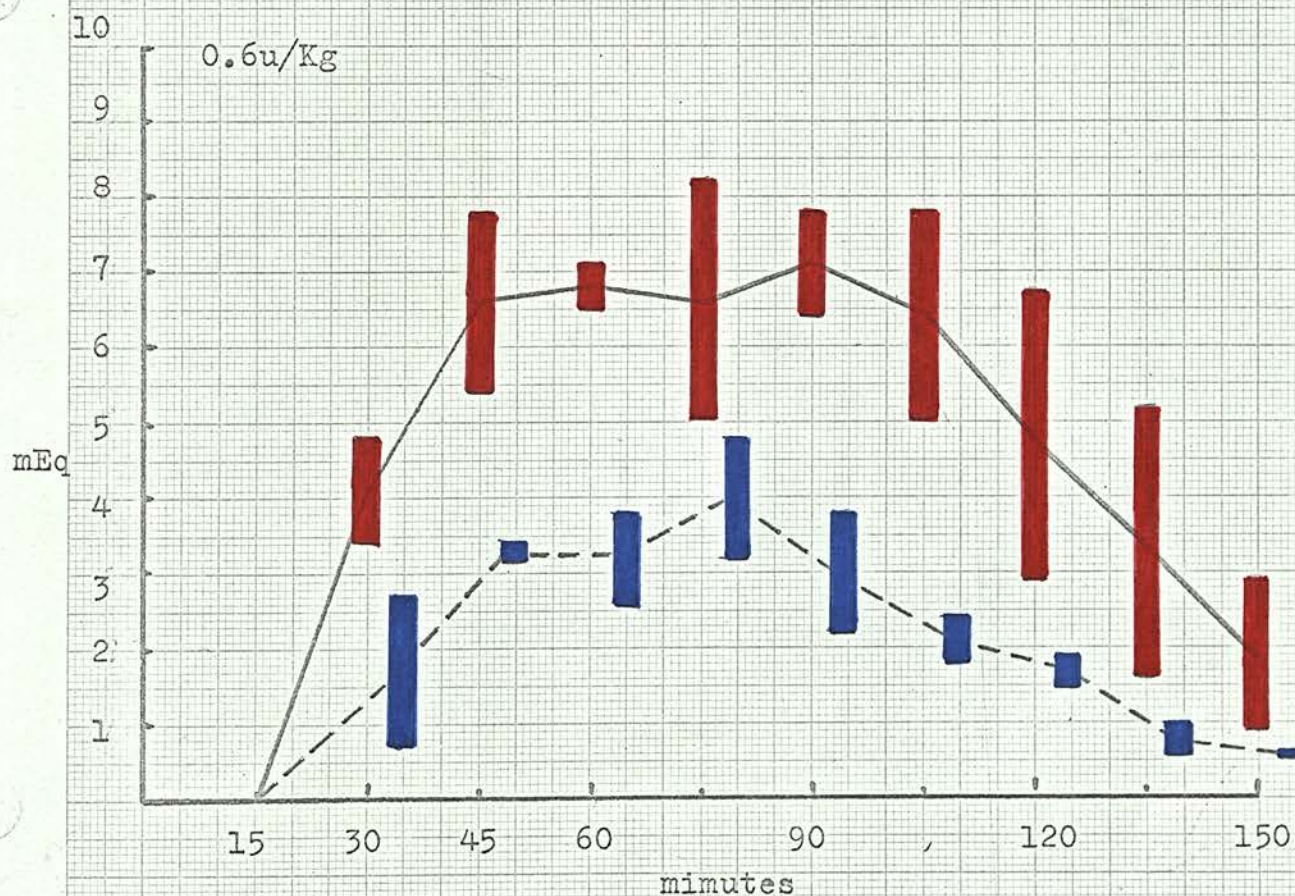
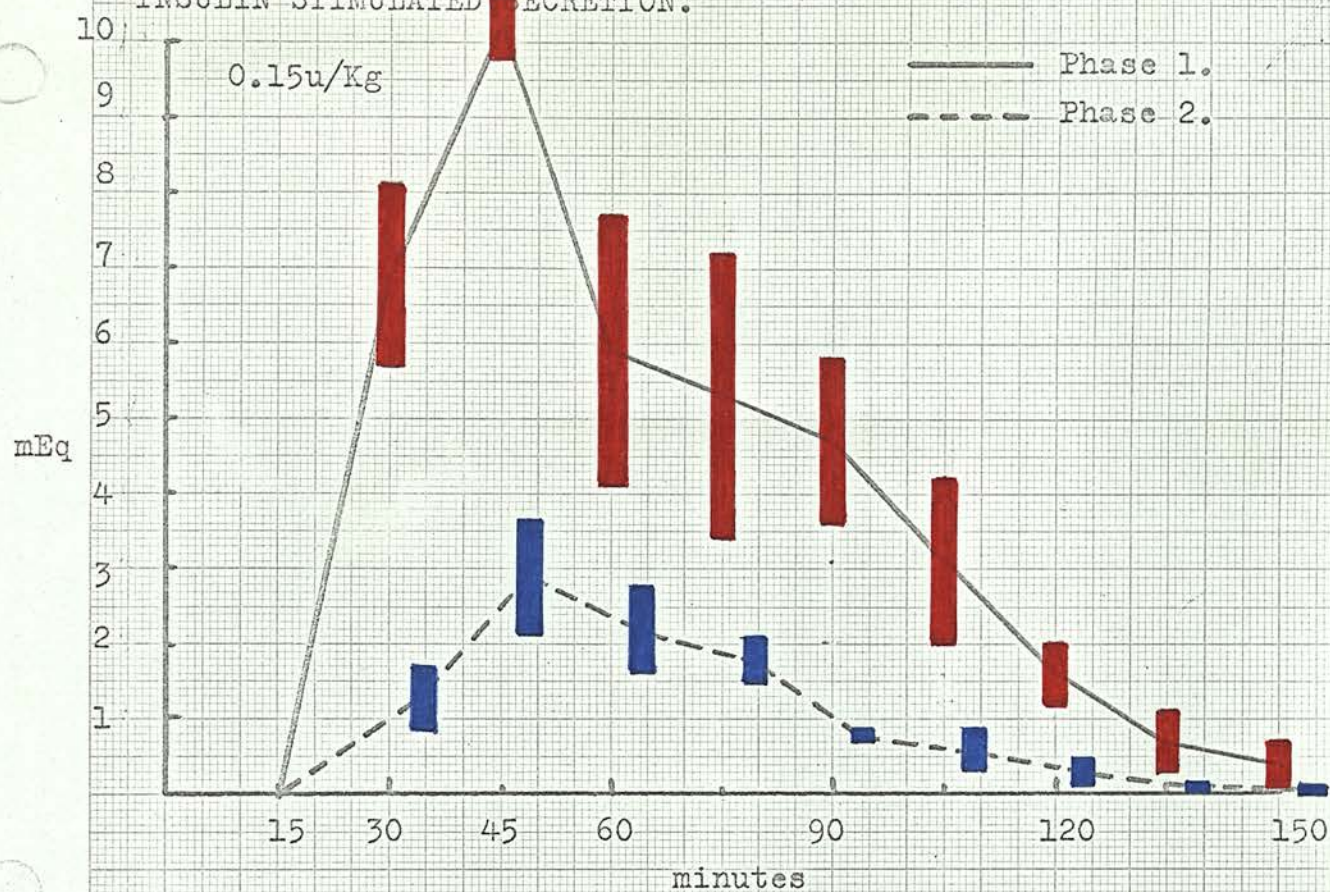


0.6u/Kg.



DOG # 68. COMPLETE ANTRECTOMY.

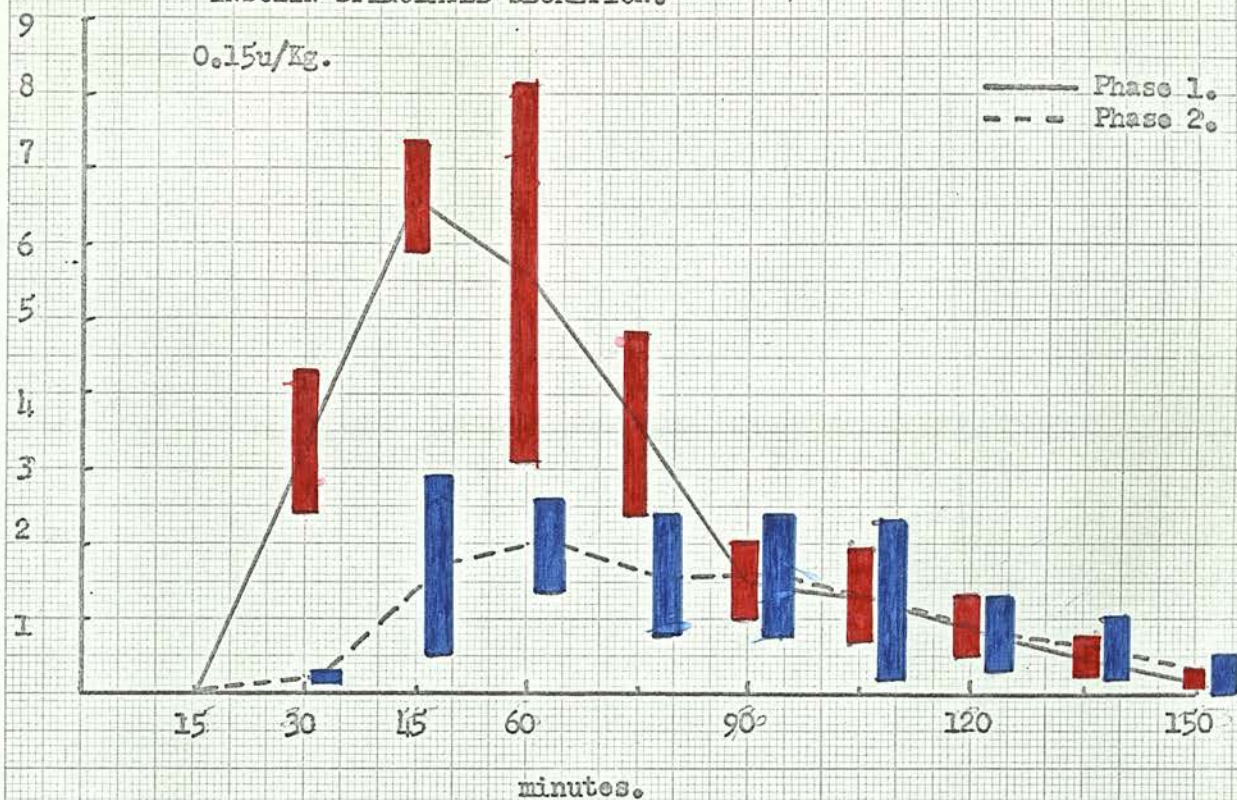
INSULIN STIMULATED SECRETION.



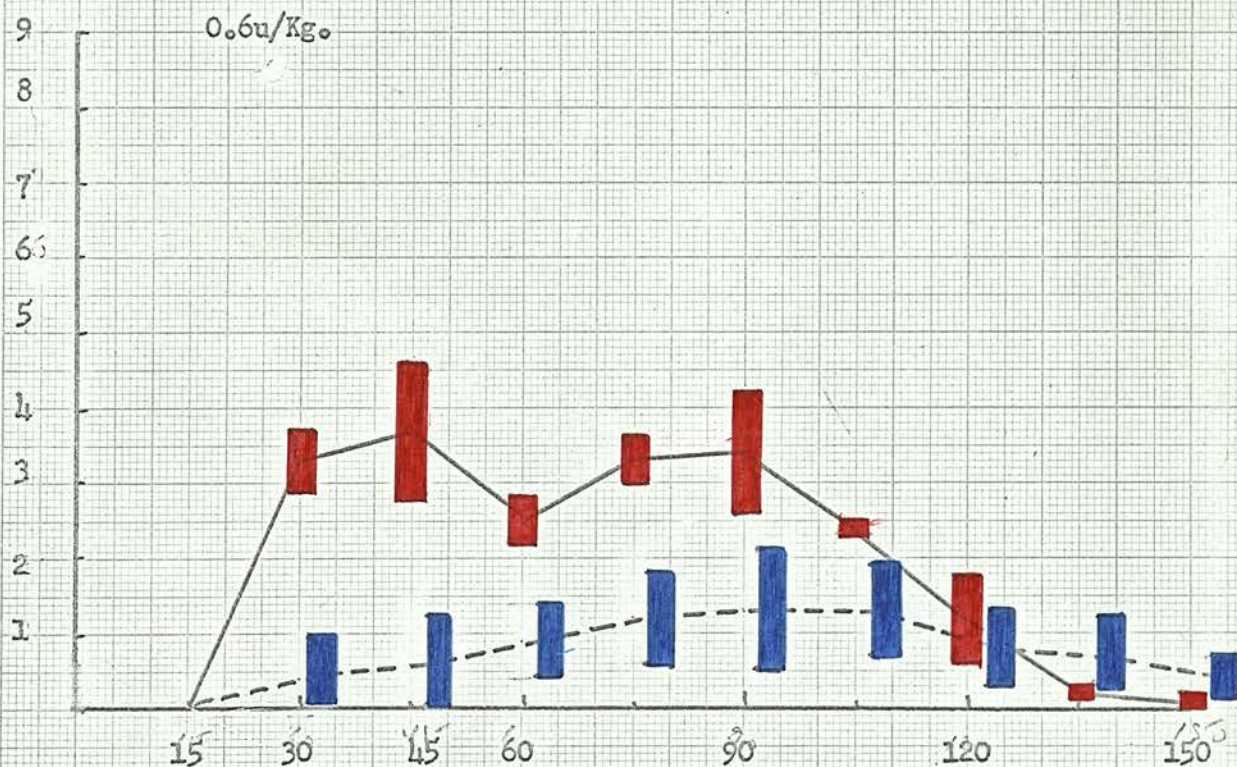
INSULIN STIMULATED SECRETION.

mEq.

0.15u/Kg.

Phase 1.
Phase 2.

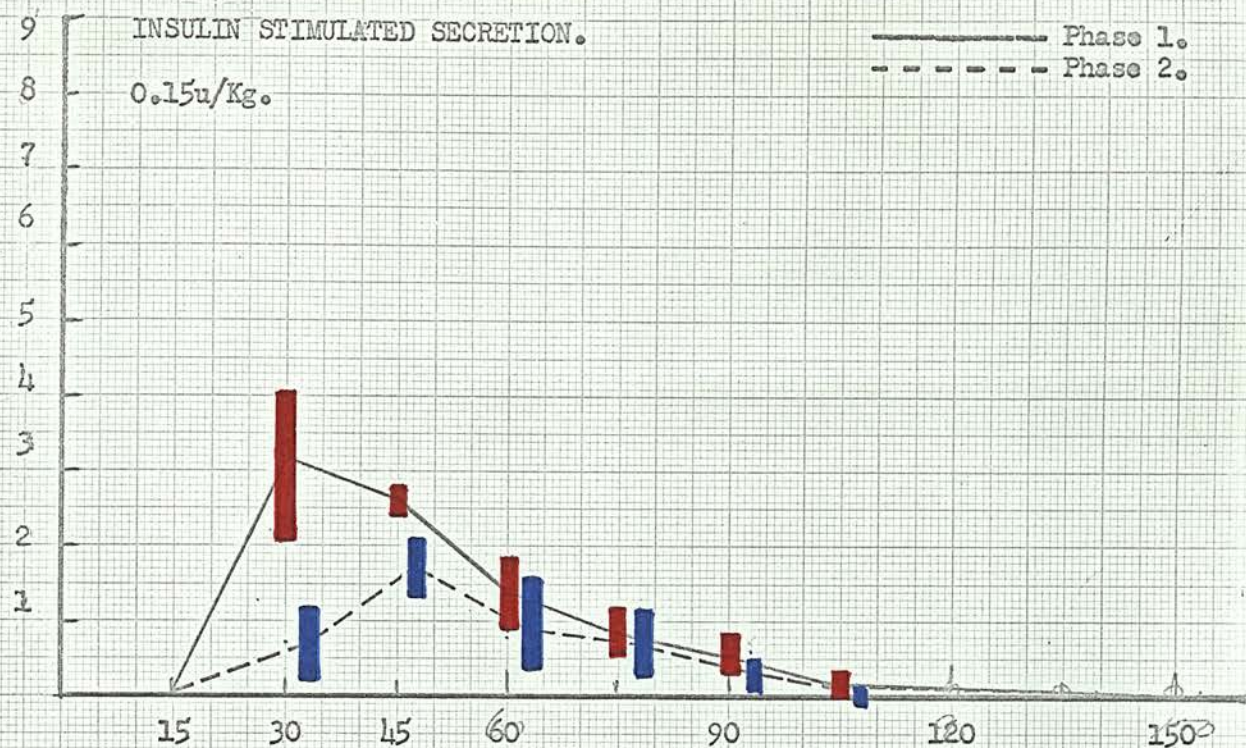
0.6u/Kg.



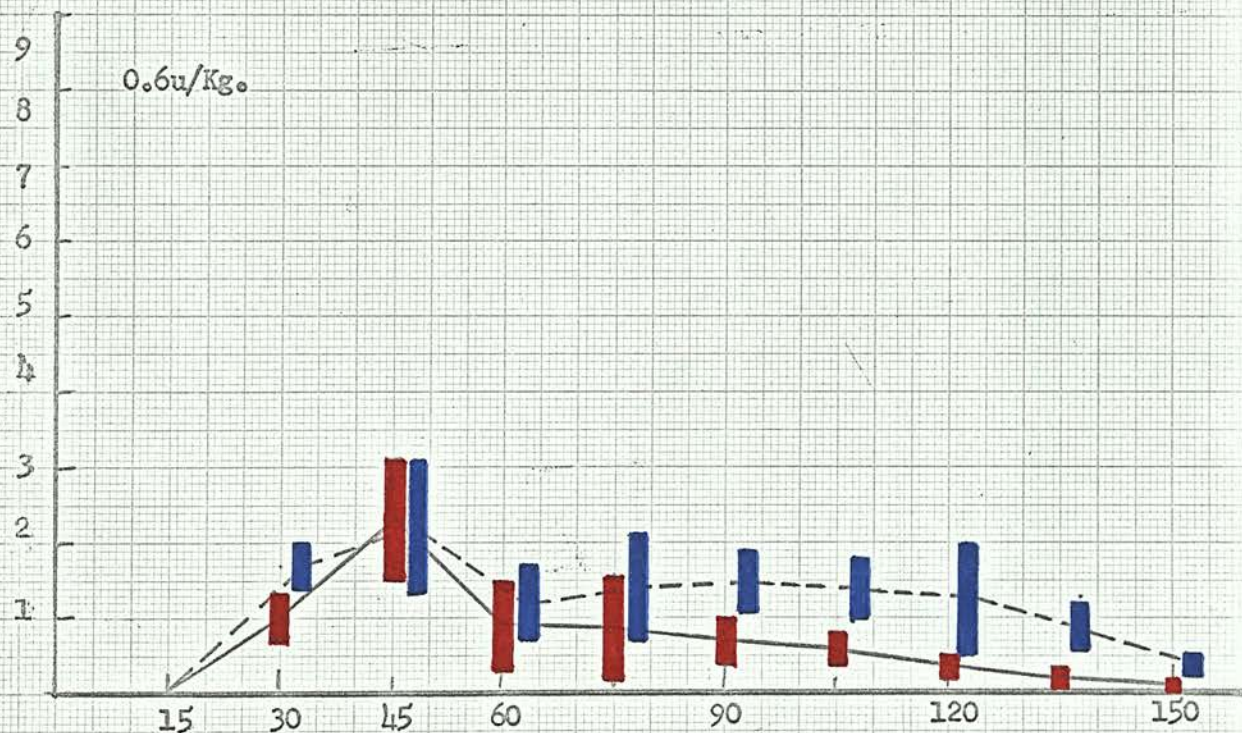
DOG # 219. SUBTOTAL ANTRECTOMY.

INSULIN STIMULATED SECRETION.

0.15u/Kg.

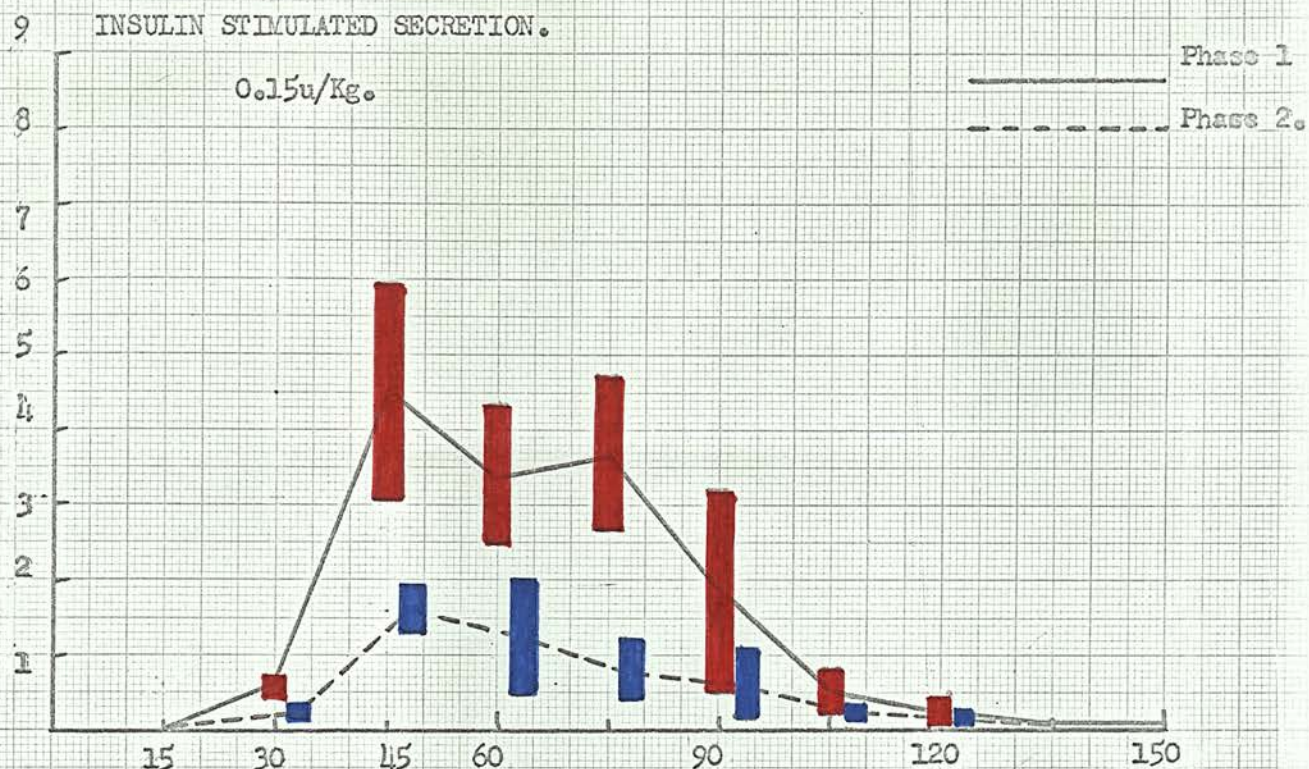
Phase 1.
Phase 2.

0.6u/Kg.

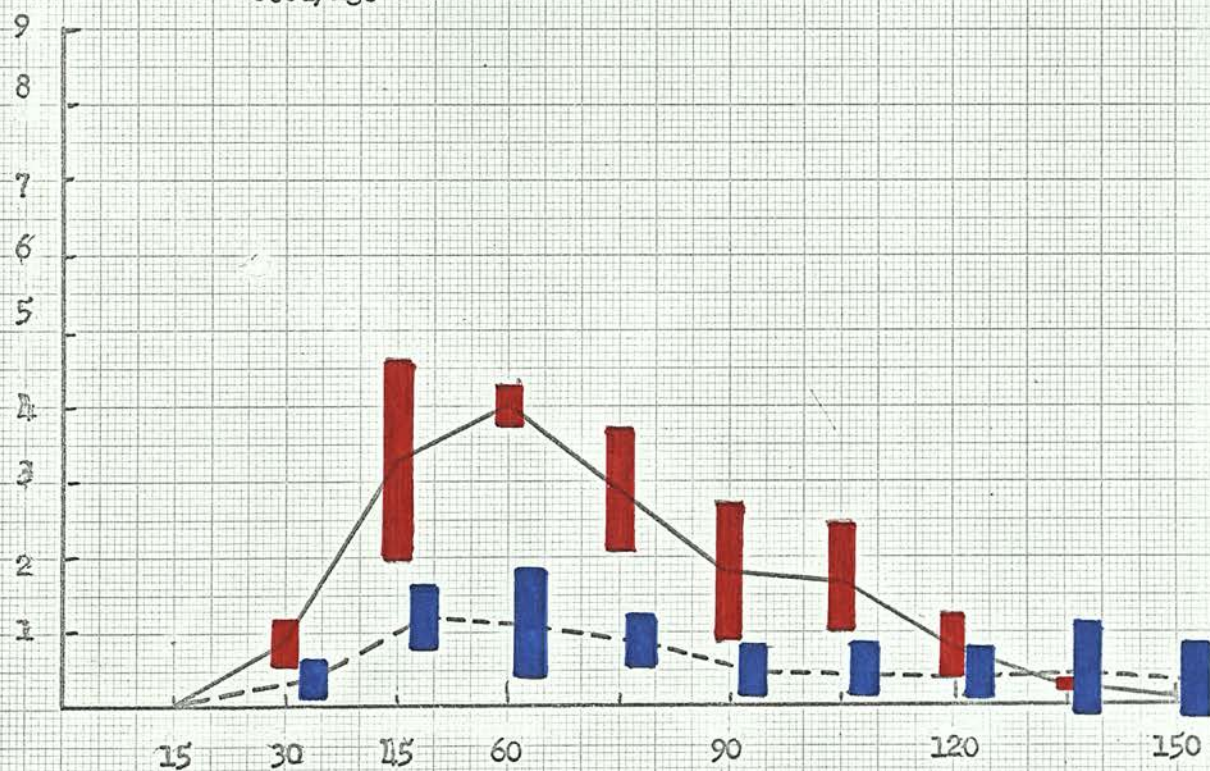


INSULIN STIMULATED SECRETION.

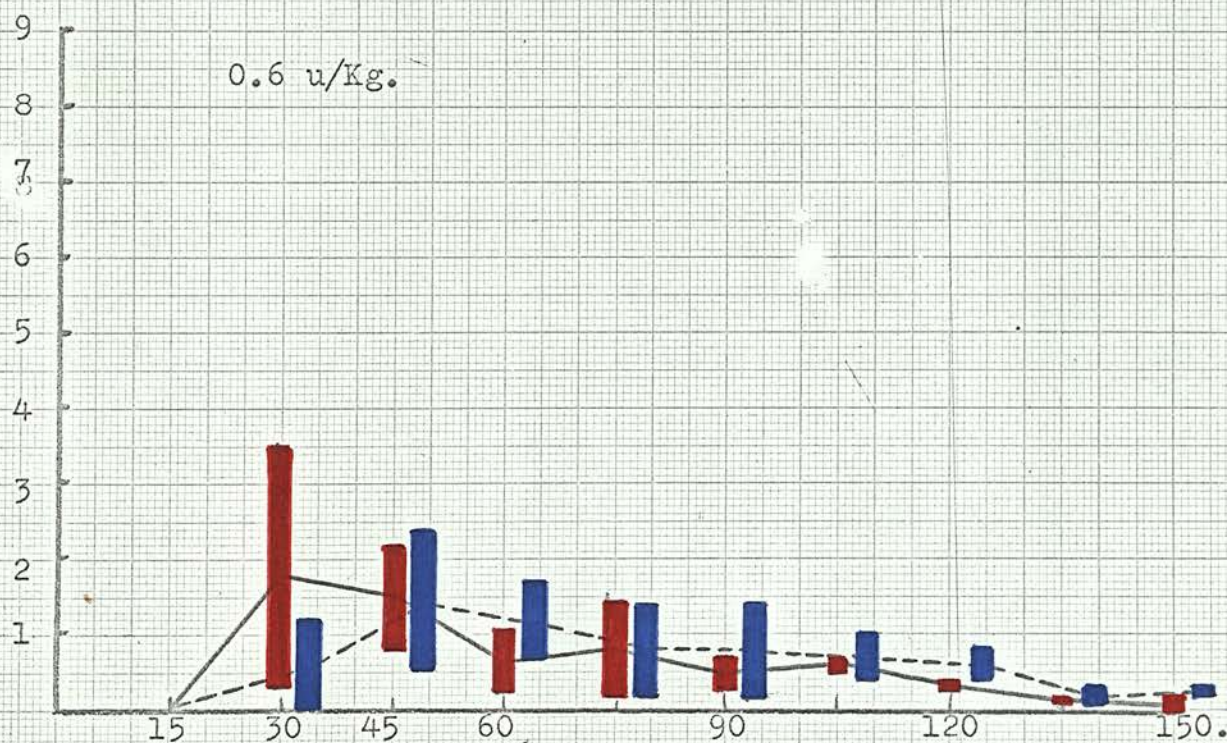
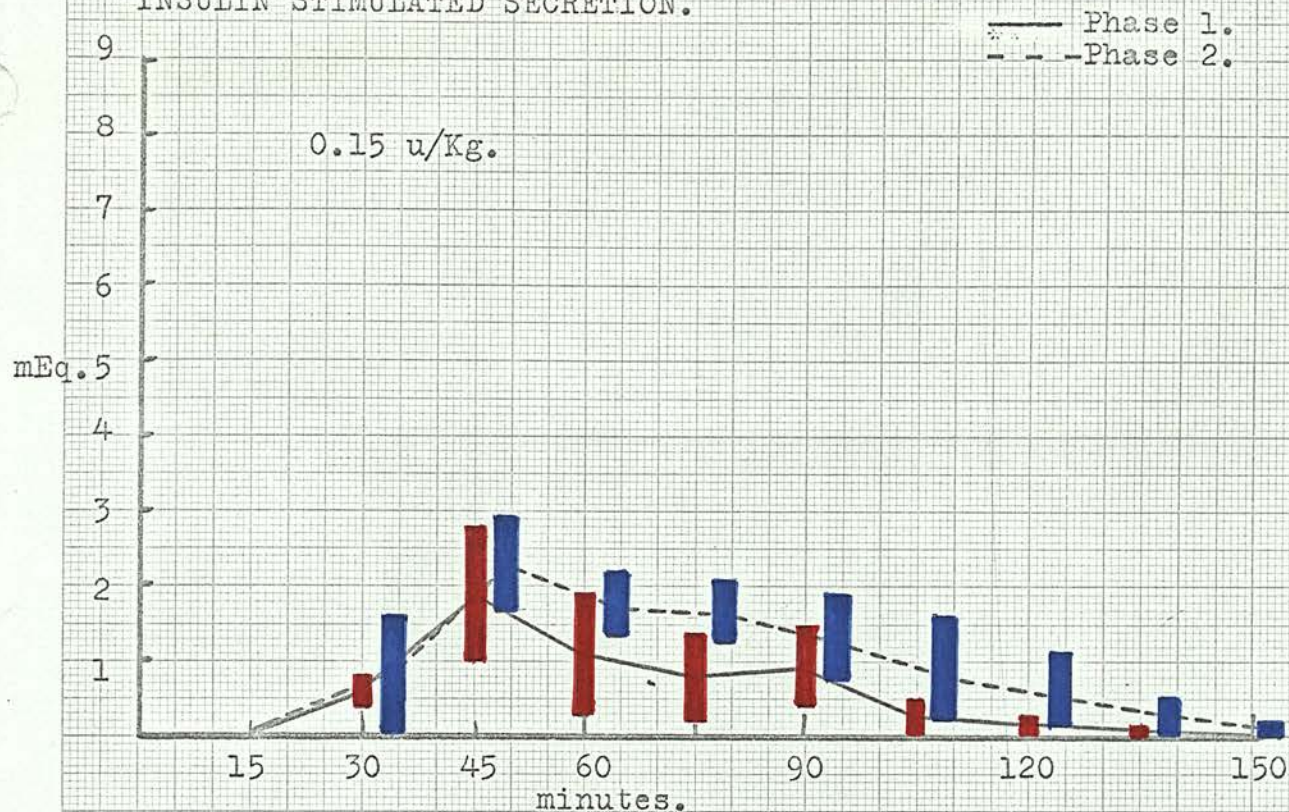
0.15u/Kg.



0.6u/Kg.



INSULIN STIMULATED SECRETION.



APPENDIX V

A SLIDING SCALE FOR INSULIN DOSAGE

AT 0.15 units/kg. BODY WEIGHT

APPENDIX V. A SLIDING SCALE FOR INSULIN DOSEAGE IN THE INSULIN
SECRETION TEST. 0.15 units/kg CALCULATED TO THE NEAREST 0.5 OF A UNIT.

PATIENT'S WEIGHTDOSE OF INSULINKgs.Units

30	4.5
30.1 - 33.0	5.0
33.1 - 37.0	5.5
37.1 - 40.0	6.0
40.1 - 43.0	6.5
43.1 - 47.0	7.0
47.1 - 50.0	7.5
50.1 - 53.0	8.0
53.1 - 57.0	8.5
57.1 - 60.0	9.0
60.1 - 63.0	9.5
63.1 - 67.0	10.0
67.1 - 70.0	10.5
70.1 - 73.0	11.0
73.1 - 77.0	11.5
77.1 - 80.0	12.0
80.1 - 83.0	12.5
83.1 - 87.0	13.0
87.0 - 90.0	13.5
90.1 - 93.0	14.0
93.1 - 97.0	14.5
97.1 - 100.0	15.0

APPENDIX VI

METHODS OF DOCUMENTATION OF

CLINICAL MATERIAL

PROFORMA: OPERATIVE AND EARLY POST-OPERATIVE DATAVAGOTOMY SURVEY.

(2nd proforma.)

Name Age (at op:) No.
 Address Date of Admission
 GP

Operation 1 Surgeon Date
 2
 3

21. OPERATIVE PATH: FINDINGS. none recorded = 0, DU = 1, GU = 2,
 GB (.....) = 4, pancreas (.....) = 5,
 other (.....) = 6.
22. ANATOMICAL FINDINGS. no op: note = 0; inadequate ditto = 1.
23. Anterior trunk: not seen = 0; single = 1; two (separate) = 2;
 two (joining) = 3;
24. Hepatic: not seen = 0; single = 1; sl: separate = 2; wide " = 3
25. Posterior trunk: not seen = 0; single = 1; double = 2.
26. Coeliac: palpated but not seen = 0; seen = 1.
27. Any other feature: no = 0, yes = 1 (.....)
28. OPERATIVE AND EARLY POST-OPERATIVE COMPLICATIONS.
 0 = none 3 = oesophagus 6 = internal or other mech: ob:
 1 = bleed 4 = stomal obst: 7 = other (.....)
 2 = spleen 5 = leak
29. ILEUS. no undue = 0; 48-72 hrs = 1; >72 hrs (.....) = 2.
30. N-G tube: no record = 0; used = 1; not used = 2; not used
 at first but had to be passed later = 3.
31. COMPLICATIONS: var: G-I
 0 = none; 2 = heartburn 4 = dumping
 1 = dysphagia 3 = vomiting 5 = other (.....)
32. DIARRHOEA. 0 = none; enough to require treatment = 1,
 max: no: stools/day: 1 - 3 = 2; 4 - 6 = 3; 7+ = 4. (.....)
33. OTHER COMPLICATIONS.
 0 = none; chest inf: (antibiotics) = 1, chest inf: (3/7 XR)
 = 2; DVT = 3; PE = 4; CT = 5; other = 6 (.....)
34. LOCAL INFECTIONS:
 0 = none 2 = wound abscess 4 = intra-perit: abs:
 1 = stitch abscess 3 = dehiscence 5 = peritonitis.
35. Duration of post-operative stay.
 10/7 or less = 1 15 - 21/7 = 3
 11 - 14/7 = 2 more than 21 = 4
36. PATHOLOGY.
 gastric and jejunal biopsies: 0 = not taken;
 1 = normal; 2 = abnormal.
37. LINE OF SECTION. 0 = not reported; 1 = complete antrectomy
 2 = incomplete antrectomy.
38. ANY OTHER POST-OPERATIVE FEATURE.
 0 = no; 1 = yes (.....)

1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17																
A				B				C				D				
<p>31. G-I COMPLICATIONS (specify reason)</p> <p>32. DIARRHOEA</p> <p>33. OTHER COMPLICATIONS</p> <p>34. ABDOMINAL INFECTION</p> <p>35. DURATION: P-O STAY</p> <p>36. PATHOLOGY</p>																
<p>21. OPERATIVE PATHOLOGY</p> <p>28. EARLY COMPLICATIONS</p> <p>OPERATION</p> <p>SURGEON</p> <p>POST-OP: ILEUS</p> <p>30. NASO-GASTRIC TUBE</p>																
<p>done N/A</p> <p>done: abnormal: 2</p> <p>done: normal: 1</p> <p>not done: 0</p> <p>(G & J Biopsies)</p> <p>21+</p> <p>15/7 - 21/7: 3</p> <p>11/7 - 14/7: 2</p> <p>10/7 or less: 1</p> <p>peritonitis: 5</p> <p>intra-perit: abscess: 4</p> <p>dehiscence: 3</p> <p>wound abscess: 2</p> <p>stitch abscess: 1</p> <p>none: 0</p> <p>() other: 6</p> <p>CF: 5</p> <p>FB: 4</p> <p>DVT: 3</p> <p>chest: XR-proven: 2</p> <p>chest: antibiotics: 1</p> <p>none: 0</p> <p>7+/d: 4</p> <p>4-6/d: 3</p> <p>stools 1-3/d: 2</p> <p>enough to treat: 1</p> <p>none: 0</p> <p>() other: 5</p> <p>Suppump: 4</p> <p>Vomiting: 3</p> <p>heartburn: 2</p> <p>dysphagia: 1</p> <p>none: 0</p> <p>ditto but passed later: 3</p> <p>(specify reason)</p>																
<p>no record: 0</p> <p>DU: 1</p> <p>GU: 2</p> <p>HH: 3</p> <p>GB: 4</p> <p>pancreas: 5</p> <p>() other: 6</p> <p>none recorded: 0</p> <p>bleed: 1</p> <p>spleen: 2</p> <p>oesophagus: 3</p> <p>stomal obstruction: 4</p> <p>leak: 5</p> <p>() other: 6</p> <p>TV+pyl: 1</p> <p>TV+GE: 2</p> <p>TV+PG: 3</p> <p>SV+pyl: 4</p> <p>SV+GE: 5</p> <p>SV+PG: 6</p> <p>SV or TV alone: 7</p> <p>CWAF: 1</p> <p>WPS: 2</p> <p>ANS: 3</p> <p>CVR: 4</p> <p>() other: 5</p> <p>no undue ileus: 0</p> <p>48-72hrs: 1</p> <p>more than 72hrs: 2</p> <p>no record: 0</p> <p>tube used: 1</p> <p>no tube used: 2</p>																

PUNCH CARD FOR RECORDING OPERATIVE AND EARLY

POST-OPERATIVE DATA

PROFORMA: LATE POST-OPERATIVE FOLLOW-UP

VAGOTOMY FOLLOW-UP 2. Card 2

Cross-refer: 1. Surgeon; operation & year and early post-op: diarrhoea.

NAME..... Hosp: No:.....

	6/12	6/12-1	3	< 5	<10	10
51. Patient pleased overall; 0=no; 1=yes.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
52. <u>VISICK</u> : 1 = 1; 3 = 3s; 5 = 4;	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
2 = 2; 4 = 3u; 6 = N/A.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
53. <u>DIGESTIVE S/s</u> : 5 = bile vomiting;	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
0 = none; 6 = food vomiting;	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
1 = dysphagia; 7 = reflux/regurg;	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
2 = flatulence; 8 = heartburn;	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
3 = early dumping; 9 = pain (.....)	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
4 = late dumping; (.....)	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
54. <u>BOWELS</u> : Change with operation?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
0=no; 1=yes; loose; 2=yes: constipation.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
55. USUAL NUMBER OF STOOLS PER DAY (.....)	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<u>DIARRHOEA</u> :	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
56. Max. no of stools per day. (.....)	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
57. <u>TYPE</u> .	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
0 = N/A, 3 = explosive;	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
1 = continual; 4 = incontinent;	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
2 = periodic; 5 = pale.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
58. IF PERIODIC: between attacks:	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
1 = normal; 2 = loose.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
59. Troublesome to patt: 0=no; 1=yes.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
60. Usual free interval (wks)	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
61. Longest free interval (wks)	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
62. Usual length of attack (days)	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
63. Longest length of attack (days)	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
64. ANY OTHER POST-OPERATIVE PROBLEM?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
0 = no; 1 = yes -- specify.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
65. <u>FURTHER GASTRIC SURGERY REQD</u> : (May also	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
have been noted on page 1)	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
0 = none; 5 = pyl. to ge.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
1 = re-vagotomy; 6 = BI to BII	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
2 = drain: to resect: 7 = BII to BI	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
3 = higher resect: 8 = add GE.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
4 = GE to pylor: 9 = other; specify.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
66. Cholecystectomy: 0 = no;	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
1 = before vagy.; 2 = after vagy.:	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
67. Cholecystogram: 0 =no, 1=before, 2=after.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
68. FAECAL FAT (3/7 stool) N/A = 0	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
early post-op = 1; late post-op = 2 (spec)	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<u>SECRETION TESTS</u>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
69. <u>IST</u> 0 = N/A; 1 = early p-o; 2 = later.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
70. <u>MAO</u> . 0 = N/A;	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
1 = Hist: early 3 = pept: early.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
2 = Hist: later. 4 = pept: later.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
71. <u>RECURRENT ULCER</u> : 0 = no; 1 = suspected;	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
2 = proven.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
72. Willing for IST.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>		

1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17																
A (YEARS) B C D																
73. TIME OF F-U (specify)																
Yes = 1																
No = 0																
64. Other post-op problems																
Yes = 1																
No = 0																
59. Troublesome to patient																
Loose = 2																
normal = 1																
58. If periodic Between attacks.																
pale = 5																
explosive = 4																
incontinent = 3																
periodic = 2																
continual = 1																
N/A = 0																
57. Type of diarrhoea (recorded)																
N/A = 0																
56. Max no: stools/d																
DIARRHOEA.																
yes to const = 2																
yes to loose = 1																
no = 0																
54. BOWELS: CHANGE c OPERATION																
7+ = 7																
4-6/day = 6																
Stools: 1-3/day = 5																
Enough to treat = 4																
none = 3																
DIARRHOEA. (page 1)																
32. EARLY POST-OP:																
WEIGHT.																
N/A. UP. DOWN. SAME.																
51. Patient pleased																
No																
52. VISICK																
Yes																
* 1=1																
2=2																
s 3=3																
u 3=4																
4=5																
N/A=6																
XX																
HOW LONG SINCE OPERATION																
6/12/12																
10/12/12																
10/12/12																
OPERATION AND YEAR.																
(Page 1) T.V. & Pyl.																
T.V. & GE.																
Year. T.V. & PG.																
S.V. & Pyl.																
S.V. & GE.																
S.V. & PG.																
S.V. or T.V. alone.																
SURGEON.																
(Page 1) C.W.A.F.																
W.P.S.																
A.N.S.																
C.V.R.																
(specify) OTHER.																
53. DIGESTIVE S/S.																
none																
dysphagia																
flatulence																
early dumping																
late dumping																
bile vomiting																
food vomiting																
reflux/regurg:																
heartburn																
pain.																